PROSPECTIVE STUDY OF HIGH DOSE RATE BRACHYTHERAPY IN CERVICAL CANCER TREATMENT USING COBALT-60 RADIONUCLIDE SOURCE

INSTITUTION

DEPARTMENT OF RADIOTHERAPY

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CERTIFICATE

This is to certify that the dissertation entitled **"PROSPECTIVE STUDY OF HIGH DOSE RATE BRACHYTHERAPY IN CERVICAL CANCER TREATMENT USING COBALT-60 RADIONUCLIDE SOURCE"** submitted by Dr.MEENAKSHI.S.B, in partial fulfillment for the award of the degree of Doctor of Medicine in Radiotherapy by the Tamil Nadu Dr.MG.R. Medical University, Chennai is a bonafide record of the work done by her in the Department of Radiotherapy, Madras Medical College during the academic year 2016-2019.

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Place :
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DECLARATION

I solemnly declare that the dissertation titled " **PROSPECTIVE STUDY OF HIGH DOSE RATE BRACHYTHERAPY IN CERVICAL CANCER TREATMENT USING COBALT-60 RADIONUCLIDE SOURCE.''** was done in department of radiotherapy, Madras Medical college and Rajiv Gandhi Government General Hospital, Chennai during June 2017 to September 2018 under guidance and supervision of Prof. Dr .N. V .KALAIYARASI.

The dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical UNIVERSITY towards the fulfilment for the award of M.D. Degree (Branch IX) in Radiotherapy.

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CONTENTS

INTRODUCTION

Cancer cervix is the second commonest malignancy among women, globally and accounts for nearly 500,000 cases and 250,000 deaths annually. According to ICMR 2012 Chennai metropolitan ranks first compared to other metropolitan with 236 per 100,000.Average annual number of cases have been on a rise since 2012. Over 80% of patients present in locally advanced stage. Around 80,000 deaths were reported due to cervical cancer in India. Radiotherapy is an effective treatment modality for carcinoma of uterine cervix. Radiotherapy in carcinoma cervix comprises usually of a combination of external beam radiation and intracavitary brachytherapy. The curative potential of radiotherapy is greatly enhanced by intracavitary brachytherapy. There are three methods for intracavitary brachytherapy dose delivery system - Low dose rate (LDR), medium dose rate and High dose rate (HDR) with pros and cons for each system. The success of brachytherapy depends on the delivery of high radiation dose to the uterine cervical tumor volume and considerable sparing of surrounding normal structures. HDR brachytherapy was developed to overcome the potential disadvantages of LDR brachytherapy radiation exposure to medical personnel, prolonged treatment time, mandatory hospitalization. HDR brachytherapy although used successfully for over 30 years, the primary disadvantage of HDR brachytherapy is the potential late toxicity of large dose per fraction. But still late tissue complications can be minimized more effectively in HDR than in LDR brachytherapy because greater normal tissue

displacement (bladder -anteriorly and rectum-posteriorly) is possible because of shorter treatment time and available retraction devices.

Several studies (including randomized and non-randomized prospective clinical trials survey of published studies and meta-analysis) have compared LDR-BT with HDR-BT in the management of cervical cancer[2]. In summary these have demonstrable comparable local control, survival and morbidity. RTOG, GOG have incorporated HDR as a component in the treatment of cancer cervix. With 5 year survival rate after radiotherapy in the range of 30% to 50% even for advanced cases of carcinoma cervix, brachytherapy with EBRT has become the standard of care .For HDR various dose fraction schedules have been used worldwide. Though iridium 192 has been widely used as a radionuclide source, in our institute it was our first time using cobalt 60 radionuclide source for treatment. Though there has been an apprehension of toxicity due to its higher energy [average-1.25MeV], studies have proved that the two radionuclide sources have comparable physical and dosimetric properties. Due to their similarity in properties the clinical outcomes on toxicity are comparable with an additional advantage of less number of change of source for cobalt 60.

LITERATURE REVIEW

EPIDEMIOLOGY

There is a wide geographical variation in incidence of cancer cervix. The highest incidence rates are reported from Asia, South America and Africa. Most of the women belong to lower socioeconomic stratum.

RISK FACTORS[3]

The predisposing factors include

- Early Sexual intercourse
- Multiple sexual partners
- HPV, HIV (Human immunodeficiency virus), HSV (Herpes simplex virus but controversial).
- Smoking

Natural History:

Squamous cell carcinoma of the uterine cervix originates at the squamocolumnar junction (transformation zone) of the endocervical canal. The lesion is frequently associated with severe cervical dysplasia and carcinoma in situ usually progressing over 10 to 20 years. The malignant process breaks through the basement membrane of the epithelium and invades the cervical stroma. The lesion may eventually manifest as superficial ulceration, exophytic tumor in the ectocervix, or extensive infiltration of the endocervix. Later on the

tumor may spread to the vaginal fornices or to the paracervical and parametrial tissues with eventual direct invasion of the bladder, rectum or both. Lymphatic metastasis depends on the stage of the tumor. Distant metastasis commonly involves lung, spine, and supraclavicular node.

Clinical Presentation

- CIS and early invasive carcinoma can be detected before it becomes symptomatic by cytological smears.
- Frequent and first manifestation of cancer cervix is post coital bleeding which may increase to metrorrhagia or menorrhagia.
- Sero sanguineous or yellowish foul-smelling discharge is also noted.
- Fatigue, weakness related to anemia if chronic bleeding occurs.
- Pain in pelvis or hypogastrium due to tumor necrosis or associated ,pelvic inflammatory disease
- Lumbosacral pain due to para aortic node involvement
- Hematuria, rectal bleeding may appear due to bladder or rectal invasion by the tumor.

PATHOLOGY

Over 90% of tumors are squamous cell carcinomas. There are 3 types:

- large cell keratinizing
- non-keratinizing

- Small cell type.

They are sub divided according to the degree of differentiation into well, moderately or poorly differentiated. Verrucous carcinoma is a variant of a very well differentiated SCC which has a tendency to occur locally but not to metastasize.

Adenocarcinoma arises from the cylindrical mucosa of the endocervix or the mucous secreting endocervical glands. Approximately they form 7-10% of cervical tumors. Mucinous is the most common sub type. Other sub types are clear cell adenocarcinoma, adenosquamous carcinoma, adenoid cystic carcinoma, and adenoid basal cell carcinoma. Small cell carcinoma, neuroendocrine tumors, undifferentiated carcinomas, lymphomas and sarcomas are also reported rarely[4].

STAGING [AJCC- 8th edition][5]

T category	FIGO	T criteria
Tx		Primary tumor cannot be assessed
T0		No evidence of tumor
T1	I	Cervical carcinoma confined to cervix
T1a	I A	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5 mm measured from the base of the epithelium and a horizontal spread of 7mm or less .vascular space invasion ,venous or lymphatic does not affect classification.
T1a1	IA1	Measured stromal invasion of 3mm or less in depth and 7mm or less in horizontal spread.
T1a2	IA2	Measured stromal invasion of more than 3mm and not more than 5mm with a horizontal spread of 7mm or less.
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2.Includes all macroscopically visible lesions, even those with superficial invasion.
T1b1	IB1	Clinically visible lesion 4cm or less in greatest dimension.
T1b2	IB2	Clinically visible lesion more than 4cm in greatest dimension.
T2	II	Cervical carcinoma invading beyond the uterus but not to the pelvic wall or to lower third of the vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension

T category	FIGO	T criteria
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extending to the pelvic sidewall* and/or involving the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney
T3a	IIIA	Tumor involving the lower third of the vagina but not extending to the pelvic wall.
T3b	IIIB	Tumor extending to the pelvic wall and/or causing hydronephrosis or nonfunctioning kidney.
T4a	IVA	Tumor invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis (bullous edema is not sufficient to classify a tumor as T4).

The pelvic sidewall is defined as the muscle, fascia, neurovascular structures and skeletal portions of the bony pelvis. On rectal examination, there is no cancer-free space between the tumor and pelvic sidewall

Definition of Regional Lymph Node (N)

N category	FIGO	N criteria
Nx		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1		Regional lymph node metastasis

Definition of Distant Metastasis (M)

M Category	FIGO	Stage M Criteria
M0		No distant metastasis
M 1	IVB	Distant metastasis

STAGE GROUPING

WHEN T is	AND N is	AND M is	Then STAGE GROUPING IS
T1	Any N	M0	I
T1a	Any N	M0	IA
T1a1	Any N	M0	IA1
T1a2	Any N	M0	IA2
T1b	Any N	M0	IB
T1b1	Any N	M0	IB1
TIb2	Any N	M0	IB2
T2	Any N	M0	II
T2a	Any N	M0	IIA
T2a1	Any N	M0	IIA1
T2a2	Any N	M0	IIA2
T2b	Any N	M0	IIB
T3	Any N	M0	IIII
T3a	Any N	M0	IIIA
T3b	Any N	M0	IIIB
T4	Any N	M0	IV A
Any T	Any N	M1	IVB

PROGNOSTIC FACTORS

PATIENT FACTORS

AGE

The study conducted by Delaloye et al[6] says that, age is not a prognostic factor in carcinoma of the cervix. But Dattoli et al[7] reported decreased survival in women younger than 35 or 40 years, who have a greater frequency of poorly differentiated tumors.

TUMOUR VOLUME

Piver and Chung[8] showed a greater incidence of lymphatic and distant metastasis and lower survival rates in patients with bulky and barrel-shaped stage IB and IIA tumors treated by radical hysterectomy. A higher incidence of pelvic recurrences and distant metastases and a decreased survival rate were reported by Fletcher[9] , Eifel et al[10]. , and Perez et al[11] in patients with larger tumors treated with irradiation. In stages IB and IIA, higher radiation doses or combination with an extrafascial hysterectomy improved local tumor control[12,13,14.].

ANEMIA

The strongest evidence that anemia plays a causative role in pelvic recurrence comes from a small randomized study conducted by Princess Margaret Hospital[15] .In all patients, the hemoglobin level was maintained at least 10 gm%, but in patients in the treatment arm, the hemoglobin level was maintained, through the use of transfusions, at least 12.5 gm%. The loco

regional recurrence rate was significantly higher for the 25 anemic patients in the control arm than it was for the patients who received transfusions.

Treatment related factors

There is higher chance of recurrence if the duration of treatment is more than 7 Weeks[16]

OVERVIEW OF TREATMENT POLICY IN CANCER CERVIX

All the three standard modalities of oncology namely radiation, surgery and chemotherapy have stamped their role in the treatment of different stages of the disease.

ROLE OF SURGERY IN CANCER CERVIX THERAPY

The role of radical surgery is limited to pre-invasive and early stages of invasive growth. In some selected cases it is combined with RT and used as a salvage procedure to treat local failure after RT. Radical curative surgery can be done up to FIGO stage IIA which has 5 year survival rates similar to radiation alone. In early disease surgery is preferred over RT in:

- Patients with Carcinoma in situ, severe dysplasia
- Small volume disease (<4cm),
- Young patients for better preservation of sexual life.
- Endocervical cancers and adenocarcinomas,
- Patients with co-existing diseases like uterus, ovarian cysts and prolapse.

Types of surgeries in carcinoma cervix[17]:

Radical hysterectomy - Excision of the uterus en bloc with the parametrium (i.e., round, broad, cardinal, and uterosacral ligaments) and the upper one-third to one-half of the vagina. There are 5 types of radical hysterectomies

- Total (extrafascial) abdominal hysterectomy (class I) consists of removal of the cervix and adjacent tissues as well as a small cuff of the upper vagina in a plane outside the pubocervical fascia. There is minimal disturbance of the ureters and the trigone of the bladder.
- In modified radical extended hysterectomy (class II), the cervix and upper vagina are removed, including paracervical tissues, and the ureters are dissected in the paracervical tunnel to their point of entry into the bladder. This operation may be performed with or without lymphadenectomy.
- Radical abdominal hysterectomy (class III) with bilateral pelvic lymphadenectomy consists of a wider resection of the parametrial tissues to the pelvic wall, with dissection of the ureters and mobilization of the bladder as well as the rectum to allow for more extensive removal of tissues. Also, a vaginal cuff of at least 2 to 3 cm is always included in the procedure. A bilateral pelvic lymphadenectomy is usually carried out. This operation is often referred to as the Wertheim or Meigs procedure.

More extensive radical hysterectomies (class IV and V) have been described, but they are rarely performed.

MICROINVASIVE CARCINOMA (STAGE IA)

The standard treatment for patients with stage IA1 disease is cervical conization or total (type I) or vaginal hysterectomy. [18]The risk of lymph node metastasis in minimally invasive carcinoma cervix is less than 1%. Because of this prophylactic lymphadenectomy is not recommended[19,20]. For patients whose tumors invade 3 to 5 mm into the stroma (FIGO stage IA2), the risk of nodal metastases is approximately 5%. Therefore, in such patients, a bilateral pelvic lymphadenectomy should be performed in conjunction with a modified radical (type II) hysterectomy. Modified radical hysterectomy is a less extensive procedure than a classic radical (type III) hysterectomy.

Stage IB and IIA Disease

Early stage IB cervical carcinomas can be treated effectively with combined external-beam irradiation and brachytherapy or with radical hysterectomy and bilateral pelvic lymphadenectomy. The goal of both treatments is to destroy malignant cells in the cervix, para cervical tissues, and regional lymph nodes[21].

In 1997, Landoni et al[22] conducted a prospective trial comparing radical surgery with radiotherapy alone. In their study, patients with stage IB or IIA disease

were randomly assigned to receive treatment with type III radical hysterectomy or a combination of external-beam and Low-Dose Rate intracavitary radiotherapy. In the surgical arm, findings of parametrial involvement, positive margins, deep stromal invasion, or positive nodes led to the use of postoperative pelvic irradiation in 62(54%) of 114 patients with tumors 4 cm or smaller in diameter and in 46 (84%) of 55 patients with tumors measuring more than 4 cm. Patients in the radiotherapy arm received a relatively low total dose of radiation to the cervix, with a median dose to point A of 76 Gy. With a median follow-up of 87 months, the 5-year actuarial disease-free survival rates for patients treated in the surgery and radiotherapy groups were 80% and 82%, respectively, for patients with tumors that were 4 cm or smaller and 63% and 57%, respectively, for patients with larger tumors. The authors reported a significantly higher rate of complications in the patients treated with initial surgery, and they attributed this finding to the frequent use of combined-modality treatment in this group.

EXTERNAL BEAM RADIATION TREATMENT

Radiotherapy has been used successfully to treat cervical cancer for nearly a century. Most of the patients present with locally advanced stage of the disease, and nearly 70% belong to FIGO Stage IIB or III at presentation[23].

The combination of external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) has become a standard treatment modality for locally advanced cervical cancer. As with radical surgery, the goal of radical radiotherapy is to sterilize disease in the cervix, paracervical tissues, and regional lymph nodes in the pelvis. Patients are usually treated with a combination of external beam irradiation to the pelvis and brachytherapy. Clinicians balance between external and intracavitary treatment in different ways, weighting one or the other component more heavily. A homogenous dose distribution over a large volume can be achieved only by teletherapy. The external beam radiation is followed by ICA to achieve the highest local control rate possible and this sequence is also ideal in that the tumor shrinkage caused by the initial EBRT will bring the anatomy to near normal resulting in an optimal and uniform dose distribution from a subsequent ICA. EBRT is delivered before brachytherapy in patients with bulky primary tumors, exophytic bleeding tumors, necrotic or infected tumors and tumors with parametrial involvement. However brachytherapy is a critical element in the curative radiation treatment of all carcinomas of the cervix. Even relatively

small tumors that involve multiple quadrants of the cervix are usually treated with total doses of 80 to 85 Gy to point A. Although patients with small tumors may be treated with somewhat smaller fields than patients with more advanced loco regional disease, care must still be taken to adequately cover the obturator, external iliac, low common iliac, and presacral nodes[24] .

External-beam irradiation is used to deliver a homogeneous dose to the primary cervical tumor and to potential sites of regional spread. An initial course of external irradiation may also improve the efficacy of subsequent intracavitary treatment by shrinking bulky tumor and bringing it within the range of the high-dose portion of the brachytherapy dose distribution. For this reason, patients with locally advanced disease usually begin with a course of external-beam treatment. Subsequent brachytherapy exploits the inverse square law to deliver a high dose to the cervix and parametrial tissues while minimizing the dose to adjacent normal tissues[25]. Whitney et al[26,27] in the Gynaecologic Oncology Group (GOG 85) randomly assigned patients with stage IIB to IVA disease to receive either hydroxyurea or cisplatin-containing chemotherapy during external-beam irradiation. All three of the cisplatin-containing regimens in these trials produced local control and survival rates superior to those for the control arms (hydroxyurea and radiation). Keys et al[28] conducted a study in patients with stage IB tumors measuring at least 4 cm in diameter. They were randomly assigned to receive radiation alone or radiation plus weekly cisplatin before extrafascial hysterectomy. Patients who received cisplatin were more likely to

have a complete histologic response and were more likely to be disease-free at the time of preliminary analysis.

In a study conducted by the Southwest Oncology Group and the Gynecology and Oncology Group (GOG)[29], included patients who were treated with radical hysterectomy and were found to have pelvic lymph node metastases. Positive margins, or parametrial involvement. Patients were randomly assigned to receive postoperative pelvic radiation alone or combined with cisplatin and 5-FU. In the preliminary analysis, patients who received chemotherapy had a better disease-free survival rate.

The Radiation Therapy Oncology Group[30] also conducted a trial in which radiotherapy alone (including prophylactic para-aortic irradiation) was compared with pelvic irradiation plus concurrent cisplatin and 5-FU [(8-year OS (67 vs. 41%)]. This is the only study in which chemotherapy was administered during both the brachytherapy and external-beam components of treatment. The results of this trial showed significant difference in the rates of local control, distant metastasis, overall survival, and disease-free survival favoring in the treatment arm with chemotherapy.

Eifel et al (RTOG90-01)[31,32] conducted a study showed that chemo radiation followed by brachytherapy improved overall survival in locally advanced carcinoma cervix compared to external beam radiation and brachytherapy alone[8-year OS (67%vs. 41%)].

Concurrent chemo radiation is the treatment of choice for locally advanced carcinoma cervix. EBRT with concurrent chemotherapy showed consistent improvement in local disease control, distant metastasis and survival[33].

In Feb 1999 National Cancer Institute (NCI), in clinical announcement advised that Cisplatin based chemotherapy administered concurrently exhibited a marked superiority over standard radiotherapy alone regimens in locally advanced cancer cervix and that furthermore Cisplatin based chemo radiation has been the standard of treatment for this disease.

BRACHYTHERAPY

Brachytherapy is also known as internal radiotherapy, endocurietherapy or sealed source radiotherapy. It is a form of radiotherapy where a radiation source is placed inside or next to the area requiring treatment[34]. Brachytherapy procedures were initially performed by inserting the radioactive material directly into the tumor ("hot" loading), thereby exposing the physicians and caregivers to high radiation doses. Manually after loaded techniques, whereby hollow needles, catheters or applicators are first inserted into the tumor, then loaded with radioactive materials, increased placement accuracy while reducing the radiation hazards. The introduction of remote controlled insertion of sources eliminated radiation exposure to visitors and medical personnel, since the

patient was housed in a shielded room while the caregivers were in an adjacent room monitoring the patient treatment remotely[35].

PRINCIPLE OF ICA

ICA delivers a very high dose to the central tumor volume including the cervix and adjacent tissues with maximum tumor control without crossing the tolerance of surrounding normal tissue. This is possible because the normal uterus and vagina are relatively radio-resistant and tolerate relatively high doses of radiation and there is a rapid fall of dose at a distance from the cervix protecting the rectum, bladder and small bowel. Intracavitary brachytherapy can be delivered by low dose rate (LDR), moderate dose rate (MDR) and high dose rate (HDR) dose delivery systems. The dose rate of LDR is 0.4- 2Gy/ hr., MDR is 2-12 Gy/hr and HDR is > 12 Gy/hr. As many studies have demonstrated comparable local control, survival and morbidity HDR-ICA has been widely incorporated as a component in the treatment of cancer cervix.

ADVANTAGES OF HDR VS. LDR IN CANCER OF CERVIX

- Eliminates radiation exposure hazard for caregivers, visitors.
- Allows shorter treatment times: Less patient discomfort, elimination of prolonged bed rest reduces hospitalization (due to outpatient therapy), possibly allows greater displacement of nearby normal tissues (by packing or using rectal retractor) which could potentially

reduce rectal and bladder morbidity, possible to treat large number of patients in institutions having high volume of cervical cancer patients.

- Allows use of smaller diameter sources than are used in LDR-reduces the need for dilatation of the cervix and need for heavy sedation or general anesthesia is reduced, physically easier to insert applicator into the cervix.
- Makes treatment dose distribution (dwell time, dwell position) optimization possible.
- Allows integration of EBRT and HDR which can lead to a shorter overall treatment duration and potentially to better tumor control.

THE AMERICAN BRACHYTHERAPY SOCIETY DOSE RECOMMENDATIONS[36]-

1) Recommended Prescription [earlier]: Low-dose-rate prescription may be in milligram-hours or in cGy to Point A or LDR primary treatment of 45-50 Gy external-beam plus 40-60 cGy/hr to a cumulative dose of 40-45 Gy. Goal TD should be >85 Gy. High-dose-rate typically prescribed in one of the following fractionation regimes: 5.5 Gy x 5, 6 Gy x 5, 7 Gy x 4
2) Timing- All treatment, including external-beam and brachytherapy, must be completed within 56 days from initiation of treatment. High-dose-rate brachytherapy commences after 39.6 Gy or 45Gy with up to 2 fractions

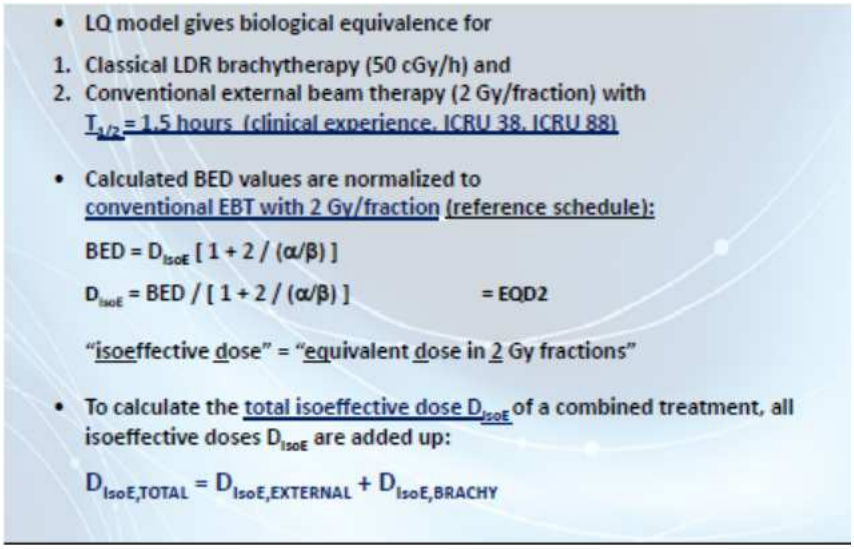
being given per week during the conclusion of external beam and during the parametrial boost portion of treatment. Brachytherapy can be initiated earlier, but not earlier than approximately 20 Gy, if the applicator placed at this time point would provide adequate tumor coverage and sparing of normal tissues. Alternatively, if 45 Gy is delivered to the whole pelvis prior to brachytherapy, two brachytherapy insertions per week should be given to avoid treatment prolongation of treatment.

3) The updated ABS 2011 Guideline recommends that 3D imaging with ultrasound, CT or MRI be performed when feasible to estimate the cervical tumor dimensions and ensure adequate coverage of the tumor. Normal-tissue dosimetry using 3D parameters results in a more accurate reflection of doses administered and may provide more reliable indicators of the risk of toxicity. The dose to point A should be recorded, the goal should be good coverage (i.e., a D90) of the involved region with EQD2 $\geq$ 80 Gy for patients with either a complete response or a partial response with residual disease less than 4 cm. For non-responders or those with tumors larger than 4 cm at the time of brachytherapy, tumor dose escalation to an EQD2 of 85–90 Gy is recommended for maximizing local control. Other fractionation regimens with EQD2 in the range of 80–85 Gy are also acceptable, although the larger fraction size, the higher the risk for normal-tissue toxicity. For the normal tissues, it is recommended that for each fraction of brachytherapy, the DVH values

are calculated and the final dose to the bladder, rectum and sigmoid calculated. Dose limits for the normal tissues are the EQD2 limit for the rectum and sigmoid is 70–75 Gy and for the bladder is 90 Gy.

CONCEPT OF EQD2

EQD2 is equivalent dose in 2gy fraction, it's the total dose in 2 gy fraction that would give the same log kill as the given schedule.



It is a more practical alternative to convert the BED to equivalent total doses delivered in 2gy fractions.

BED =nd[1+d÷α/β]

EQD2 =BED/(1+2/α/β)

SOURCES FOR HDR INTRACAVITARY BRACHYTHERAPY

A radionuclide with high specific activity (activity per unit mass; Ci/g) is needed so that treatment dose rates of at least 12 Gy/hr can be achieved without sacrificing the level of miniaturization needed to support intracavitary and

interstitial brachytherapy. A source no larger than 1 mm in diameter by 4mm long with an exposure rate of at least IR/sec at l cm is required. The exposure rate achieved by a small source depends on the chemical form (i.e. relative mass of non-radioactive atoms) of the source, its density, exposure rate constant of the radionuclide and photon self-absorption.

SOURCES

The need for high specific activity sources limits the number of radioisotopes suitable for HDR remote after loaders. Most HDR units use Iridium-192 (^{192}Ir) or cobalt 60 (^{60}Co). ^{192}Ir offer smaller source sizes but sources must be changed frequently. Most centers exchange their ^{192}Ir sources every 3 or 4 months (half life 73.8 days) whereas a similar decay fraction for ^{60}Co takes 5-8years (half life 5.26 years). ^{60}Co is used as an intracavitary HDR source in the form of small spherical pellets and it emits two high energetic gamma rays(1.17 &1.34 MeV). The smaller sources permit access to more body sites via interstitial or intraluminal applications. Based solely on specific activity considerations ^{192}Ir has been the optimal choice for HDR brachytherapy and is being widely used radionuclide for the application. With the introduction of cobalt as a brachytherapy source paradigm has shifted to its use for cost effectiveness in high burden setups.

COMPARISON BETWEEN COBALT AND IRIDIUM SOURCE

Source Specifications of cobalt and iridium source

Fig-2.1

	Cobalt-60	Iridium-192
ISO Classification 2919-1998	C 65444	C 63333
Half-life	5,27 years	73,8 days
Physical-Chemical form	solid, metal	solid, metal
Source activity	74 GBq ± 10%	370 GBq + 30%; -10%
Outer dimensions of the source: Diameter Total length of the wire:	 1 mm 2180 mm	 0,9 mm 2180 mm
Dimensions of active part Diameter: Length:	 0,5 mm 3,5 mm	 0,6 mm 3,5 mm
Working life	max 100.000 source transfers or 5 years	max 25.000 source transfers or 4 months

Fig- 2.2

The air kerma-rate-constant is almost three times higher for Co-60 than for Ir-192

Nuclide	$\bar{E}$ (MeV)	$T_{1/2}$	(Ci/g)	Γ (μGy m^2 GBq^{-1} h^{-1})	$d_{1/10}$ 1) (lead)	$d_{1/10}$ (concrete)
	mean energy	half-life	specific activity	air kerma-rate constant	tenth value layer	tenth value layer
Co-60	1.253	5,27a	330	309	4,8cm	32cm
Ir-192	0.38	73,8d	450	108	1,2cm	23cm

Co-60 vs. Ir-192: factor 2.86

Beyond 200 Kev all isotopes show similar absorption in tissues

Fig- 2.3

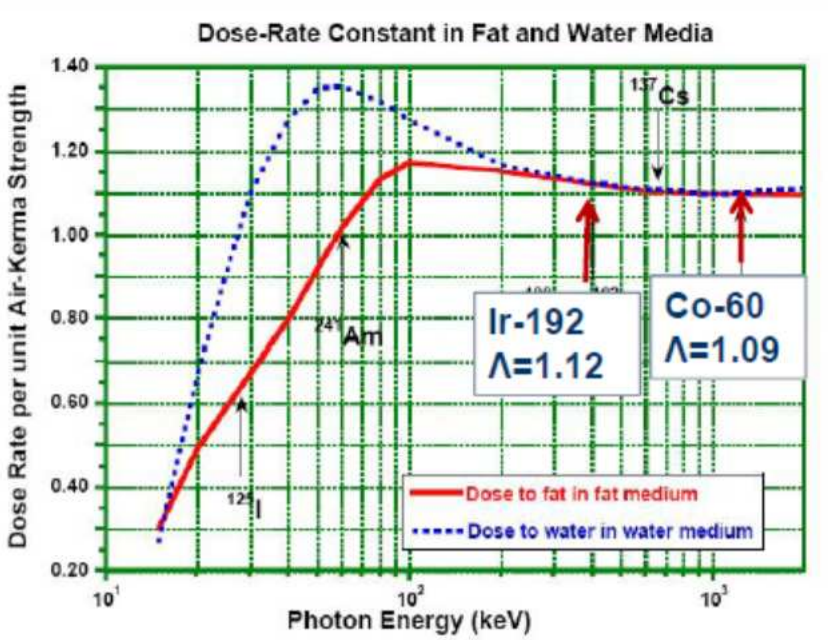


Fig- 2.4

Anisotropy- No difference between the two radio isotopes except dip in the direction of source axis.

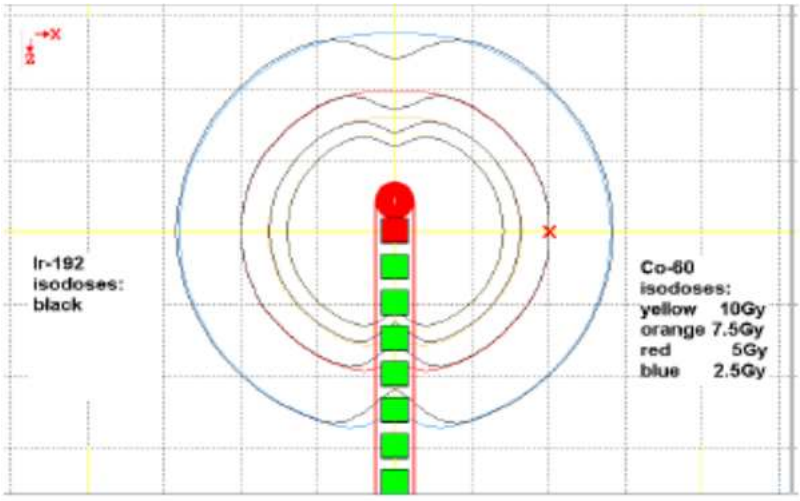
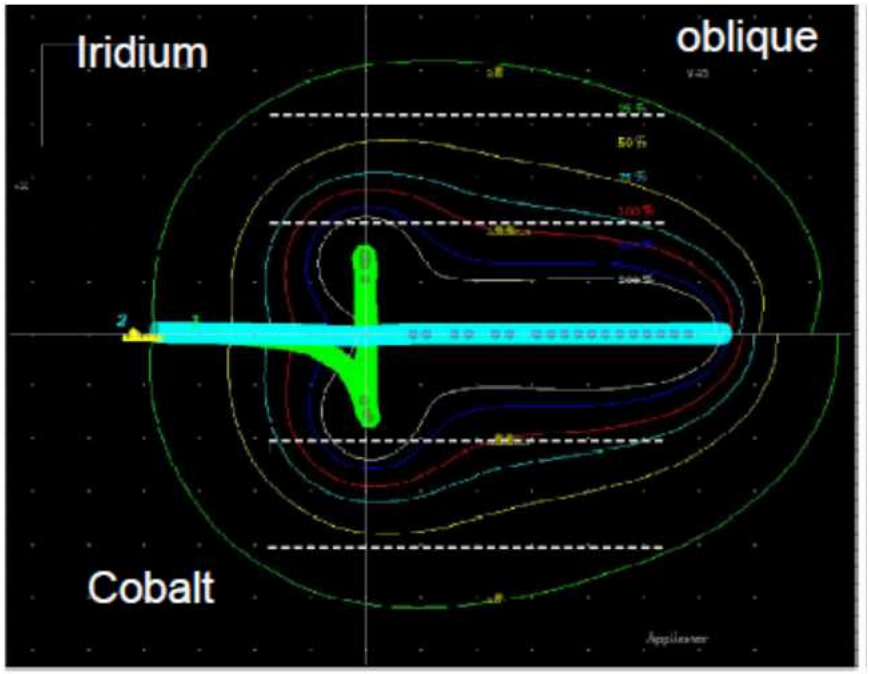
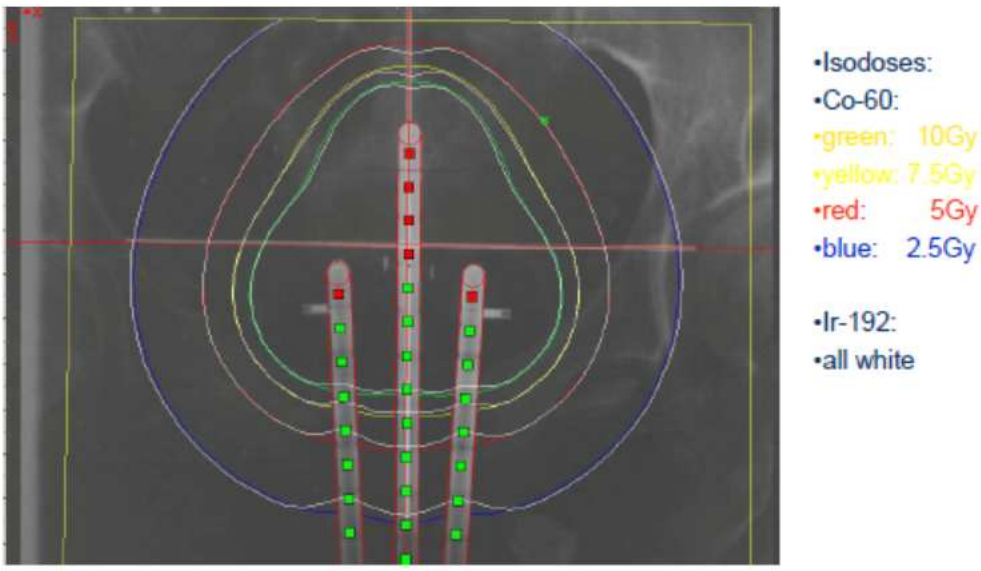


Fig -2.5



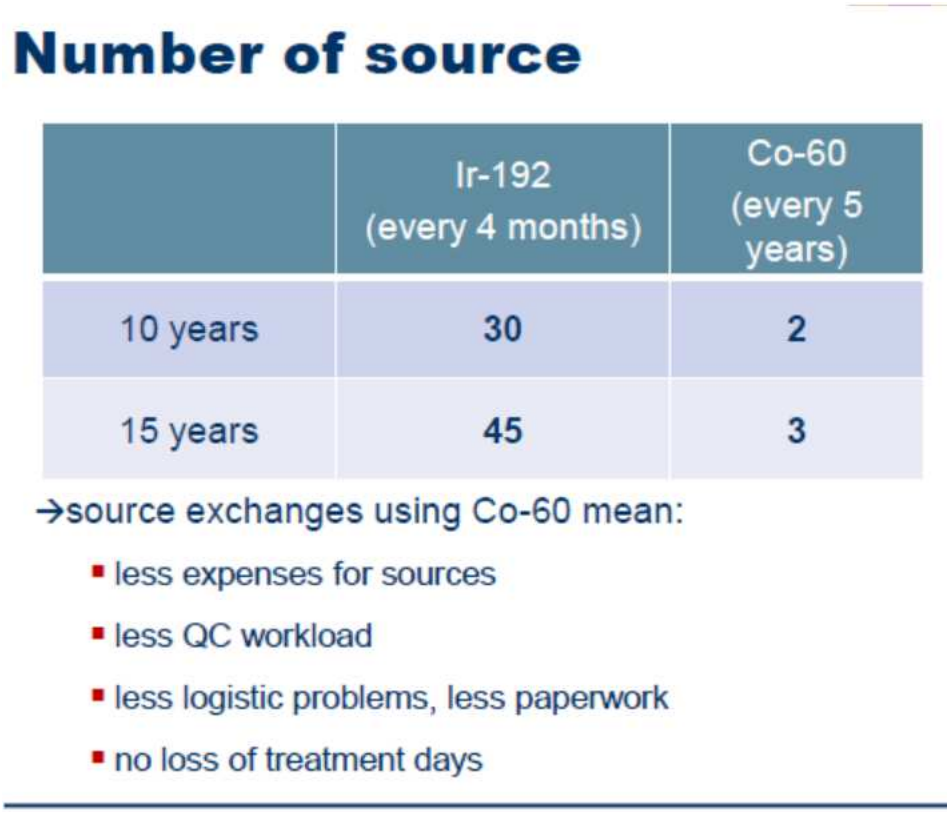
No clinical impact of using Co-60 instead of Ir-192

Fig -2.6- Isodose distribution for ^{60}Co and ^{192}Ir



No clinical impact of using Co-60 instead of Ir-192

Fig -2.7 source change data for both radionuclides



DOSE SPECIFICATION

Since the first application of radium in the treatment of cancer of the uterus in 1908, several techniques have evolved, most of which are modifications of the Stockholm technique and the Paris technique. Stockholm[37] based techniques was introduced by Forsell and Heyman' at the Radium hemmet in Stockholm. It is a fractionated course of radiation delivered over a period of one month. In Stockholm there are three insertions each of 22 hours separated by 1 -3 weeks. Total prescribed dose - 6500-7100 mg Ra and 4500 mg Ra is contributed by the vaginal box and dose rate is 110 R/hr or 2500mg/hr

per fraction. Paris technique[38] is a single application of radium for 120 hrs (45R/hr). It delivers a dose of 7000- 8000mg-hrs of radium

The Manchester system, which evolved from the Paris technique, uses a Rubber uterine tandem to hold one to three radium tubes and rubber ovoids, separated by a rubber spacer, to each hold a radium tube. The radiation is delivered in at least two applications. In the Fletcher-Suit applicator the tandem and the ovoids (or the colpostats) are made of stainless steel and then secured to hollow handles to permit after loading of the sources[39].

Brachytherapy plays a very important role in obtaining high cure rates with minimum complications. Ideal placement of the uterine tandem and vaginal ovoids produces a pear-shaped distribution, delivering a high dose to the cervix and paracervical tissues and a reduced dose to the rectum and bladder[40]. If the intracavitary placement has been optimized, this can usually be accomplished without exceeding a dose of 75 Gy to the bladder reference point or 70 Gy to the rectal reference point, doses that are usually associated with an acceptably low risk of major complications. The dose to the surface of the lateral wall of the apical vagina should not usually exceed 120 to 140 Gy. Suboptimal placements occasionally force compromises in the dose to tumor or normal tissues. To choose a treatment that optimizes the therapeutic ratio in these circumstances requires experience and a detailed understanding of factors that influence tumor control and normal tissue complications[41,42,43.]

HIGH DOSE RATE APPLICATORS

Fletcher-Suit or Fletcher-Suit-DeIco's

These applicators are used for the treatment of gynecological malignancies of the uterus, cervix and pelvic side walls. The applicator set typically consists of three rigid intrauterine tandems, with curvature of 15-, 30-, and 45-degree angles, and a pair of ovoids or colpostats. The tandem and the ovoids (or the colpostats) are made of stainless steel and then secured to hollow handles to permit after loading of the sources. CT and MRI compatible applicators are now available.

The Manchester System

The Manchester system is one of the oldest and the most extensively used systems in the world. It is characterized by doses to four points: point A, point B, a bladder point, and a rectum point. The duration of the implant is based on the dose rate calculated at point A, although the dose at the other points is taken into consideration in evaluating a treatment plan. With the availability of the treatment planning computers, most users of the Manchester system examine the isodose distributions in the frontal and sagittal planes in addition to obtaining dose at the four designated points. Point A still remains the point of dose prescription. Point A was originally defined as 2 cm superior to the lateral vaginal fornix and 2 cm lateral to the cervical canal. Later, it was redefined to be 2 cm superior to the external cervical os (or cervical end of the tandem), and 2 cm lateral to the cervical canal. Point B is defined 3 cm lateral to point A.

Ideally, a point A represents the location where the uterine vessels cross the ureter. It is believed that the tolerance of these structures is the main limiting factor in the irradiation of the uterine cervix. Point B represents obturator node.

The International Commission on Radiation Units and Measurements System [ICRU]

The ICRU has recommended a system of dose specification that relates the dose distribution to the target volume, instead of the dose to a specific point. The dose is prescribed as the value of an isodose surface that just surrounds the target volume.

Data required for reporting intracavitary therapy [ICRU-38][41]

- Description of the Technique: Minimum information should include the applicator type, source type and loading and orthogonal radiographs of the application.
- Total Reference Air Kerma: By this parameter, it is meant the total air kerma strength of sources times the implant duration. This is similar to the total milligram-hours of radium or total mg-Ra eq-h except that the sources are calibrated in units of air kerma strength, that is, ^Gy m2 h-1.
- Reference Volume. The reference volume is the volume of the isodose surface that just surrounds the target volume. The prescription isodose value of 60 Gy includes the dose contribution

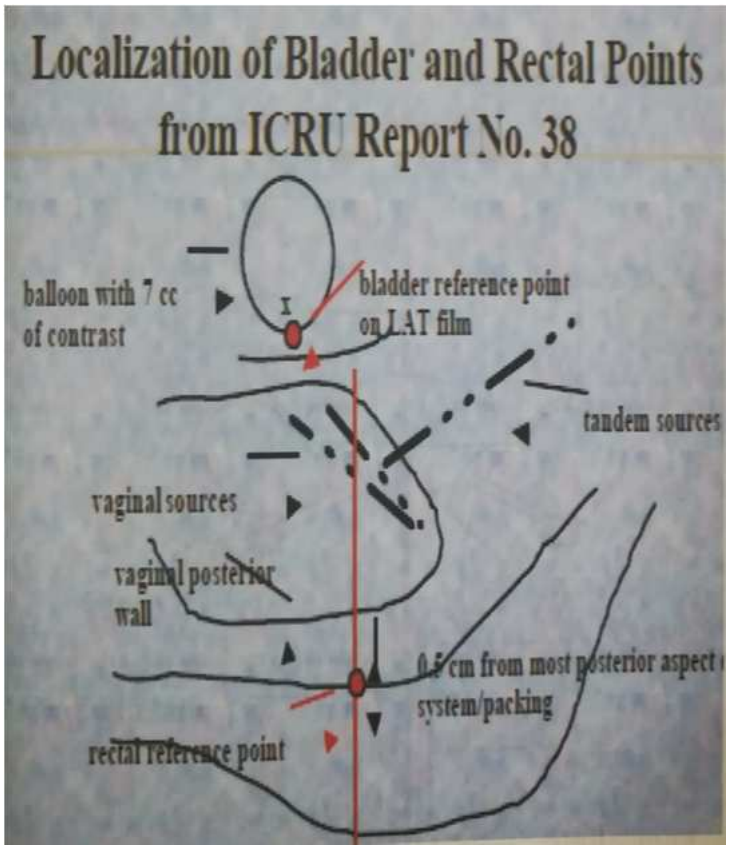
from the external beam. The reference volume for the intracavitary part of the treatment should be identified and its dimensions recorded.

Absorbed Dose at Reference Points

Bladder Point: The bladder point is localized by using a Foley catheter, with the balloon filled with 7 ml of a contrast material. On the frontal radiograph, the bladder point is marked at the center of the balloon; on the lateral radiograph, the bladder point is obtained on a line drawn antero posteriorly through the center of the balloon, at the posterior surface.

Rectal Point: The rectal point is identified on the frontal radiograph at the midpoint of the ovoid sources (or at the lower end of the intrauterine source). On the lateral radiograph, the rectal point is located on a line drawn from the middle of the ovoid sources, 5 mm behind the posterior vaginal wall. The posterior vaginal wall may be visualized by using radiopaque gauze for the vaginal packing.

Pelvic Wall Points: On the anteroposterior radiograph, the pelvic wall points are located at the intersection of a horizontal tangent to superior aspect of the acetabulum and a vertical line touching the medial aspect of the acetabulum. On the lateral view, these points are marked as the highest mid distance points of the right and left acetabulum.



CHARACTERISTICS OF AN IDEAL APPLICATION IN BRACHYTHERAPY[42]

• The ovoids should fill the vaginal fornices - largest ovoid size to be used.

• The ovoids should be separated by 0.5 -1.0 cm, admitting the flange on the tandem.

• The axis of the tandem should be central between the ovoids

• Tandem - 1/3 of the way between Sl -S2 and the symphysis pubis.

• The tandem - midway between the bladder and Sl -S2.

• Ovoids should be against the cervix (marker seeds).

• Tandem should bisect the ovoids. The bladder and rectum should be packed away from the implant.

DOSIMETRIC CHARACTERISTICS OF BRACHYTHERAPY SOURCES

In general, four factors influence the single-source dose distribution for photon-emitting sources:

- distance (inverse-square law);
- absorption and scattering in the source core and encapsulation;
- photon attenuation and
- Scattering in the surrounding medium.

RADIOBIOLOGY OF BRACHYTHERAPY AND THE DOSE-RATE EFFECT

The biological effects of radiotherapy depend on dose distribution, treated volume, dose rate, fractionation and treatment duration. These factors, have an important role in determining the outcome of external beam radiotherapy or of brachytherapy.

The biological damage inflicted by irradiation of human cells with ionizing radiation can be divided into three consecutive steps:

A very short initial physical phase (about 10^{-18} S), during which photons interact with orbital electrons, raising them to higher energy levels inside the

atoms (excitation), or ejecting some of them from the atoms (ionization). This is the energy deposition phase.

A chemical phase, again very short (about 10^{-3} s), during which ionized and excited atoms interact, leading either directly or indirectly through the formation of free radicals to the breakage of chemical bonds. Free radicals are highly reactive and can induce chemical changes in biologically important molecules like DNA. Single-strand or double-strand breaks in DNA appears to be the basic damage leading to biological effects.

A biological phase, much longer (seconds to years), during which the cells react to the inflicted chemical damage[43].Specific repair enzymes can successfully repair the vast majority of lesions in DNA. A few lesions however may not be repaired, and may therefore lead to cell death. Cell death is not immediate and usually occurs during the next cell division (apoptosis is a minor process in most human cells). The early reactions are seen during the first days or weeks after irradiation (for example diarrhea or acute mucositis). They are temporary because the cell deficit is compensated by the repopulation of stem cells, and subsequently of differentiated cells. Late reactions due to damage to the late-reacting tissues, for instance blood vessel damage, fibrosis, telangiectasia, etc., may be seen after months or years. Damage to these late reacting normal tissues is poorly repaired and is responsible for most severe complications of radiotherapy. Tolerance of these tissues is the limiting factor for radiation therapy.

THE FIVE R'S OF RADIOBIOLOGY

A number of biological processes take place during irradiation and modify the radiation response. These processes are often described as the 5 R's of radiobiology[44]

Each follows a specific time pattern:

- **Repair of DNA damage**. Both experimental and clinical studies have shown that human tumors strongly differ in radio sensitivity and radio curability thought to stem from differences in capacity for repair of sub lethal damage[45,46].
- **Reassortment or redistribution in the cell cycle**. The cell cycle is divided into four consecutive stages: Gl, S, G2 and M. Gl is a gap of apparent inactivity after a mitosis (M), before DNA synthesis (S-phase) resumes in view of the following cell division. G2 is a second gap of apparent inactivity between S phase and M.
- **Radiosensitivity** - varies along the cell cycle, S being the most resistant phase, and G2 and M the most sensitive. Therefore, cells surviving an exposure are preferentially in a stage of low sensitivity (Gl), i.e. synchronized in a resistant cell cycle phase. They progress thereafter together into S and then to the more sensitive G2 and M phases. A new irradiation exposure at this time will have a larger biological effect (more cell kill). However, while this synchronization effect has explained some

experimental results, redistribution has never been shown to play a measurable role in the clinic of radiotherapy.

- **Repopulation -** Cells surviving an irradiation keep proliferating. This increases the number of clonogenic cells, i.e. the number that must eventually be sterilized to eradicate cancer. Repopulation therefore has a detrimental effect as far as cancer control is concerned. Stem cells do also proliferate in normal tissues, which has in this case a protective effect (it helps the tissue to recover from radiation damage and it adds to DNA repair in cells).
- **Reoxygenation -** Because of an inappropriate development of intra tumoral vasculature, every tumor of clinically detectable size contains a large proportion of poorly oxygenated cells. Also, the proportion of hypoxic cells increases with the tumor size. Acutely hypoxic cells are far more radio resistant than well oxygenated cells. This is expressed by the Oxygen Enhancement Ratio (OER), i.e. the ratio between radiation doses required in hypoxia and air to produce the same biological effect. Its value is 3, and it varies very little with dose or with the biological system. Hypoxic cells usually survive irradiation, but they progressively (re)oxygenate, due to the better supply of oxygen available after well oxygenated cells have died .This restores radio sensitivity in the tumor. Several mechanisms are involved, but reoxygenation occurring at long intervals is probably due to tumor shrinkage leading to a reduction of the intercapillary distance.

DOSE RATE EFFECTS IN BRACHYTHERAPY

Biological effects of radiation are strongly dependent upon the rate of dose delivery. The radiobiological processes involved in high dose rate brachytherapy are in all respects similar to those involved in fractionated external beam radiation therapy, except for the volume effect, as mentioned earlier. Repair, repopulation, and reoxygenation, are the main factors determining outcome. They do not occur during the very short duration of irradiation (up to 10-15 minutes), but take place between consecutive fractions, provided the interval is adequate.

Repair. - For brief exposures, the survival fraction S of a cell population decreases with increasing dose D. It has been mathematically modelled as the sum of two type of lesions:

Lethal (non-repairable) lesions, with a survival fraction $S = \exp(-\alpha D)$, represented by the tangent to the survival curve at its origin.

Sublethal lesions, non-lethal and potentially repairable, but the accumulation of which can cause cell death, with a survival fraction $S = (-\beta D^2)$

The sum of these two components leads to the classical linear-quadratic

Equation proposed by Chadwick & Leenhouts and Kellerer & Rossi.

$S=\exp-(\alpha D+(\beta d^2)$.

The survival curve displayed on a semi-logarithmic graph exhibits an initial shoulder. According to the model, it is proportional to DNA repair capacity. Hence, a broad shoulder is associated with a large repair capacity. The

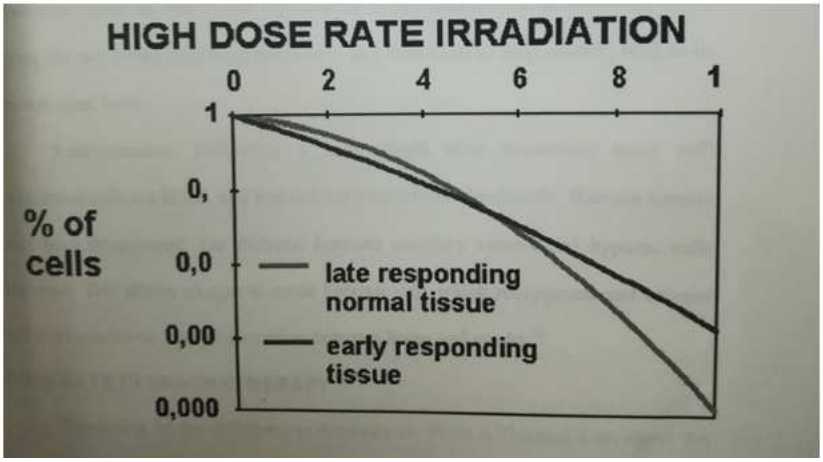
ratio α/β corresponds to the dose at which the contribution of the two factors to the survival fraction is equal, αD = βD2, and D = α/β. A large α/β corresponds to a small shoulder (small repair capacity) and a small α/β to a broad shoulder (large repair capacity).

In summary, a low α/β is characteristic of late-responding normal tissues and some tumors (0.5 to 6Gy, average 3 Gy), while a higher α/β ratio characterizes the early-responding normal tissues and carcinomas. (7 to 20 Gy, average 10 Gy

Radiobiological studies have shown that each successive fraction in a series equally effective, so the effect (E) of n fractions of size d can be expressed as:

$E= \alpha D+ \beta D^2$

Where the total radiation dose D = nd.



Repopulation does not occur in late responding normal tissue during the course of a 6-7 weeks irradiation, but it plays a role in early reactions and tumor cell killing. Proliferation has little effect in tumors for treatment times shorter

than 3-4 weeks[47] . After this time, accelerated repopulation of fast-growing tumors may be observed[48]. For early effects on skin and mucosa (desquamation and mucositis), the spontaneous tissue kinetics are unchanged until about 10 days after the initiation of Irradiation, when the rate of cell replacement is accelerated[49]. It remains very active during the two weeks following irradiation, and then tends to drop quickly, back to its physiological level.

Reoxygenation. Following a large single dose irradiation, most well oxygenated cells are killed, and hypoxic cells survive predominantly. Because aerobic cells have disappeared, the distance between capillary vessels and hypoxic cells decreases. This allows oxygen to reach hypoxic cell, which reoxygenate and become more radiosensitive. The process takes between hours and weeks[50].

COMPLICATIONS

RTOG-ACUTE TOXICITY [Table-2.1]

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
GENITO URI NARY	Frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring medication.	Frequency of urination or nocturia that is less frequent than every hour. dysuria urgency, bladder spasm requiring local anaesthetic.	Frequency with urgency and nocturia hourly or more frequently/ dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/ gross haematuria with / without clot passage.	Hematuria requiring transfusion, acute bladder obstruction not secondary to clot passage, ulceration or necrosis.	Death

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Small bowel toxicity	Anorexia with ≤5% weight loss from pretreatment baseline/nausea not requiring antiemetic's/ abdominal discomfort not requiring parasym patholytic drugs or analgesics.	Anorexia with ≤15% weight loss from pretreatment baseline/ nausea and or vomiting requiring antiemetic's/ abdominal pain requiring analgesics.	Anorexia with≥15%weight loss from pretreatment baseline or requiring NG tube or parentral support. Nausea and/or vomiting requiring tube or parentral support/ abdominal pain ,severe despite medication /hematemesis or melena/ abdominal distention[x ray demonstrating distended bowel loops]	Ileus, subacute or acute obstruction, perforation, GI bleeding requiring transfusion/ abdominal pain requiring tube, decompression or bowel diversion.	Death

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rectal toxicity	Increased frequency or change in quality of bowel habits not requiring medication/Rectal discomfort not requiring analgesics.	Diarrhea requiring parasympatholytic drugs/Mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics.	Diarrhea requiring parentral support/ severe mucous or bloody discharge necessitating sanitary pads/ abdominal distention [X-ray demonstrates distended loops]	Acute or sub acute obstruction, fistula or perforation, GI bleeding requiring transfusion, abdominal pain or tenesmus requiring tube decom pression or bowel diversion.	Death

AIM OF THE STUDY

To evaluate the acute gastrointestinal and genitourinary toxicity profile in carcinoma cervix patients using cobalt 60 radionuclide source.

SECONDARY END POINTS

- Feasibility of twice weekly brachytherapy
- Response assessment after completion of treatment.

STUDY CENTRE-

- Dept. of Radiotherapy, Barnard Institute of Radiotherapy, Madras Medical College, Chennai-3
- The study was reviewed and approved by the institutional ethical committee.

STUDY PERIOD

From June 2017 to September 2018

STUDY DESIGN – Single arm prospective study.

MATERIALS AND METHODS

CASE SELECTION

Carcinoma cervix patients who had completed their EBRT and slated for brachytherapy with minimal or no parametrial disease.

NO. OF PATIENTS - 38

INCLUSION CRITERIA

- Biopsy proven newly diagnosed carcinoma cervix
- Age - 30-65 years
- Stage – IB2 –IIIB
- Histology – Squamous cell carcinoma and its variants.
- ECOG 0-2
- Previously not exposed to any chemotherapy or radiotherapy.
- No major life threatening complications
- HIV negative
- Patient should be fit for anesthesia [GA,SA,IV sedation]
- Cystoscopy – for ruling out bladder invasion
- Urine routine, culture and sensitivity-to rule out other causes of cystitis before brachytherapy.
- Written and informed consent.

EXCLUSION CRITERIA

- Age - < 30 and > 65 years.
- ECOG -3 or more
- Stage IVA –involvement of bladder and rectum.
- Inadequate hepatic and renal functions
- Patient not consenting to chemotherapy.
- Previously treated for any other malignancy.
- Metastatic or recurrent disease
- HIV positive patients
- Patient unfit for anesthesia.

INVESTIGATIONS

- Biopsy from the tumor
- Complete blood count, liver function test, renal function test, viral markers.
- CT scan abdomen and pelvis or MRI- plain and contrast [pretreatment and post treatment at 6-8 weeks]
- Chest X ray –PA view ,ECG, blood grouping
- Cardiology evaluation for fitness.
- Weekly CBC and RFT before each fraction of brachytherapy.

DATA COLLECTION AND METHODS

Eligible patients treated with radiotherapy in the form of external beam radiotherapy to a total dose of 45-50Gy to the whole pelvis. [45-50Gy/180-200 cGy/#/25#/5 days a week [Monday to Friday] using cobalt teletherapy machine.

Followed by brachytherapy to a dose of 21Gy/7 Gy/#/3# with a minimum gap of 72 hours between each fraction using cobalt 60 source with BEBIG BRACHYTHERAPY MACHINE.

CONCURRENT CHEMOTHERAPY

Cisplatin 40mg/m2 weekly along with proper premedication.

Patients to be clinically assessed during treatment for toxicity of acute gastrointestinal and genitourinary symptoms and response graded accordingly. CT abdomen and pelvis or MRI to be taken 6-8 weeks post treatment for response assessment. Toxicity to be graded according to RTOG acute toxicity criteria. Patients were also assessed for their compliance during brachytherapy sessions.

TREATMENT PLANNING

EBRT

The whole pelvis including cervix, vagina, and parametrium with the iliac and pelvic lymph nodes treated.

RT PORTALS AND BORDERS

SUPERIOR - L4-L5 interspace [to include iliac and hypogastric nodes]

INFERIOR – If vagina uninvolved –lower border of obturator foramen.

If vagina involved- entire vagina upto introitus was included.

LATERAL- 2cm lateral to bony pelvis.

Treatment field was verified using X-ray simulation

PORTALS

AP and PA portals treated if field separation was less than 20cm

Field separation of more than 20cm were treated with 4 field box technique where the anterior border was kept in front of pubic symphysis and posterior border at S2-S3 junction.

CHEMOTHERAPY DRUG - cisplatin

DOSE - 40mg/m2 –weekly

SCHEDULE - Weekly once

PREMEDICATIONS – Inj.Dexamethasone

Inj.Ranitidine

Inj.Ondansetron

With adequate hydration before and after chemotherapy.

INTENT OF ADDING CHEMOTHERAPY - Radio sensitizer.

TOTAL NUMBER OF CYCLES - 4 -5 cycles

INTRACAVITARY PROTOCOL

After Teletherapy all patients were assessed for intracavitary application. Those who were found fit for brachytherapy were subjected to the procedure.

HDR BRACHYTHERAPY

Technique - Remote after loading with cobalt 60 source.

Machine - BEBIG

Activity - 1.82 curie [67.484 GBq]

Intracavitary applicator – Modified fletcher suit with 15 and 20 degree angulation.

No. of fractions -3 # with a minimum gap of 72 hrs between each fraction.

Dose prescribed to Point A - 7Gy.

PROCEDURE

Under anesthesia [IV sedation/SA/GA] with patient in lithotomy position the perineum and upper half of thighs were cleaned with beta dine and draped. Per vaginal examination done .Urinary bladder was catheterized and 7ml of diluted contrast(3ml of contrast +4 ml of distilled water) was injected into the Foleys balloon. Uterine sound was introduced and uterine length measured. The cervical stopper was adjusted according to the uterine length and fixed. Then the two ovoids were introduced and positioned accordingly .Adequate vaginal

packing was done. Rectal tube inserted. CT simulation was done. The films were used in our treatment planning system for applicator reconstruction, defining Point A, Point B, dose prescription to point A and calculating bladder and rectum points as per ICRU38 .Dose to bladder and rectum was kept less than 80% of point A. Optimization done using change in dwell position and time .After obtaining the desired prescription isodose, patient was connected to the BEBIG machine with cobalt 60 source through catheters (transfer tubes) and treated.

The Assessment of GI and GU toxicities was done as per schedule

First assessment -after the application of first HDR ICRT brachytherapy

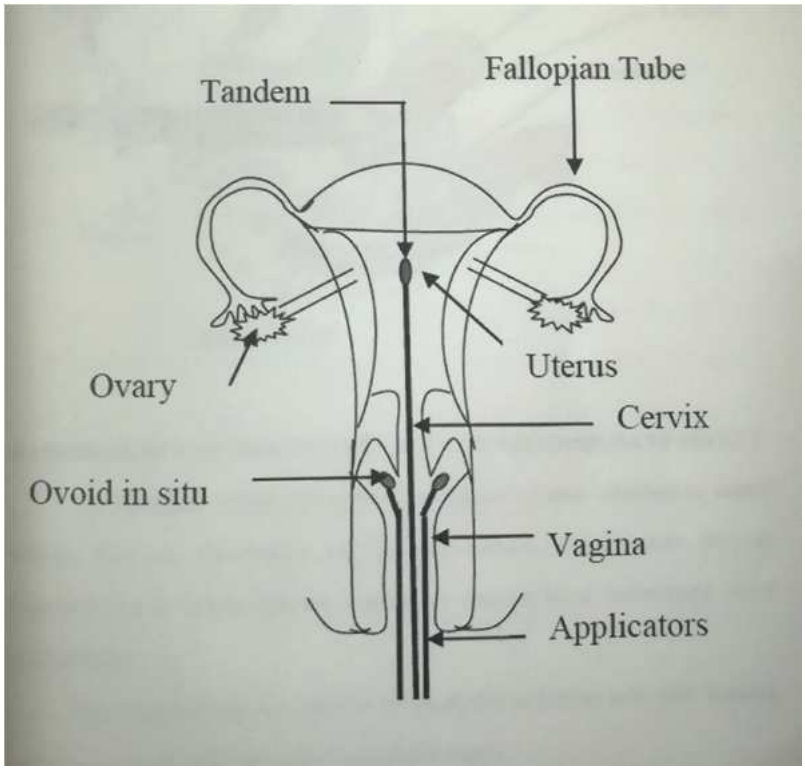
Second assessment – at the time of last HDR ICRT application

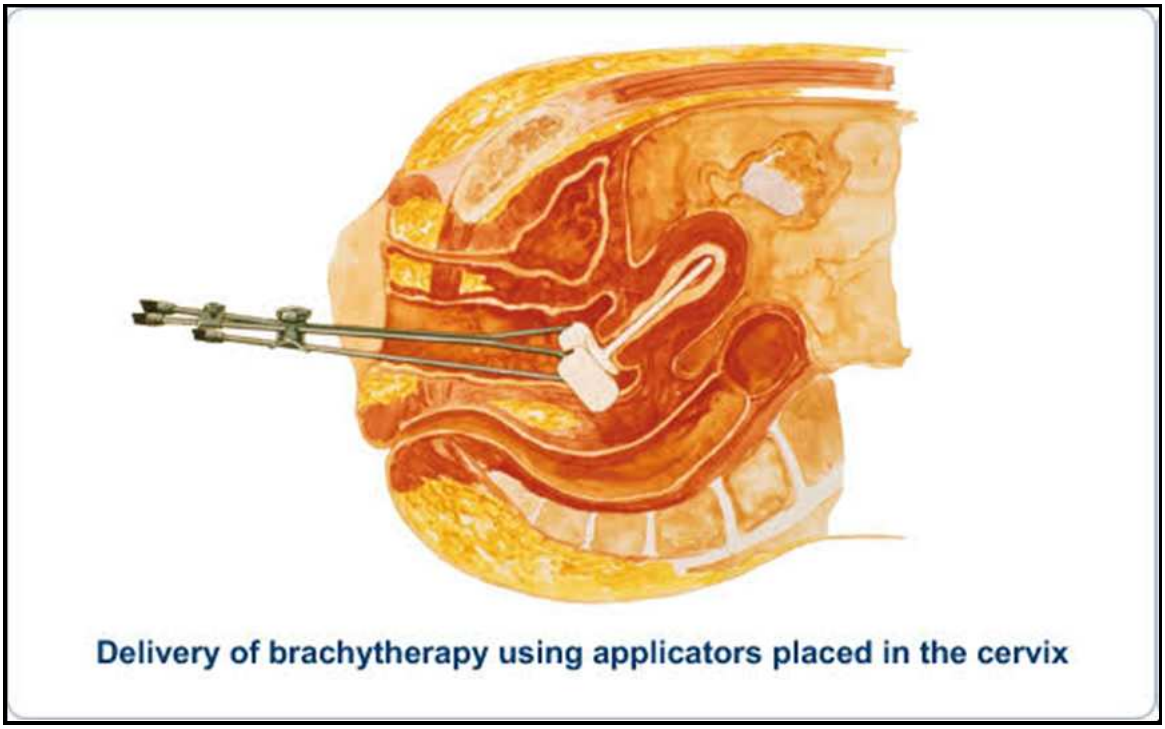
Third assessment- one month later to last HDR ICRT application

Fourth assessment-two month later to last HDR ICRT application

Fifth assessment- three month later to last HDR ICRT application

ANATOMICAL TOPOGRAPHY AND BRACHYTHERAPY APPLICATOR INSERTIONS. [Fig -4.1]





FLETCHER SUIT DELCLOS APPLICATOR [Fig - 4.3]

BEBIG HDR BRACHYTHERAPY MACHINE [Fig -4.4]

SIMULATION FILMS [AP VIEW] -fig -4.5

Fig – 4.6 [LATERAL VIEW]

ISODOSE DISTRIBUTION IN AP AND LATERAL VIEW

Fig – 4.7

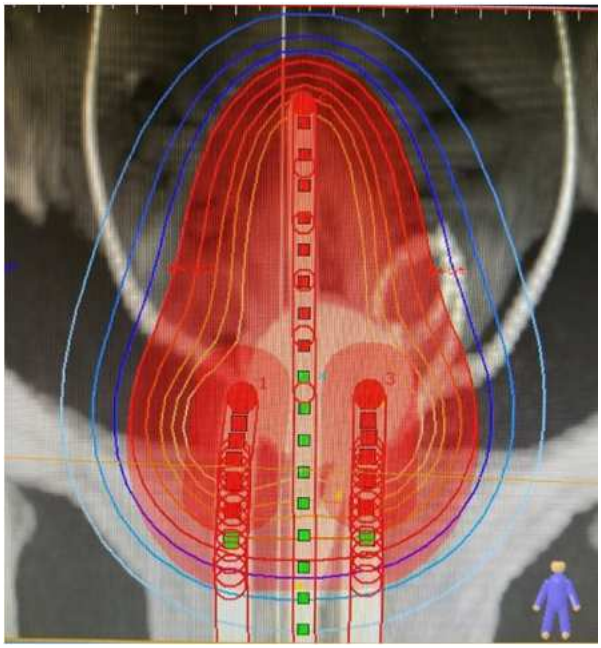
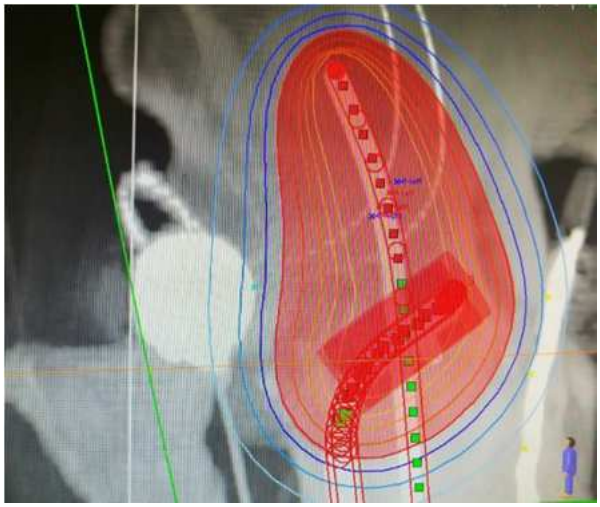


Fig-4.8



CASE ANALYSIS AND RESULTS

STUDY POPULATION AND COMPLIANCE TO TREATMENT

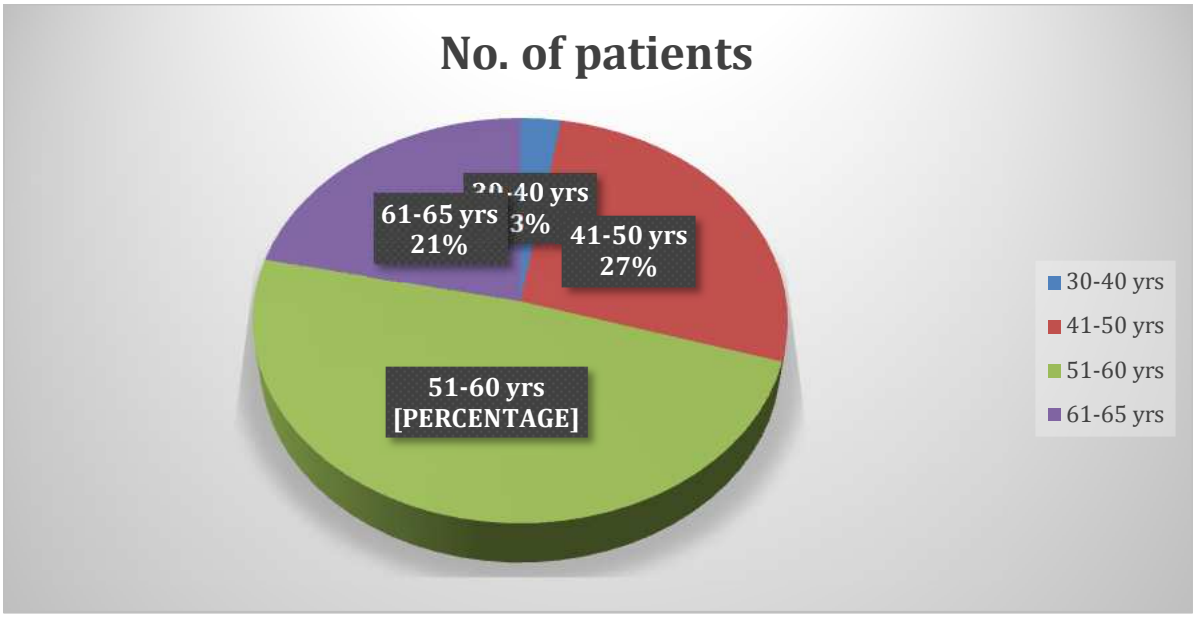
From June 2017-September 2018 a total of 38 patients of carcinoma cervix were studied for acute toxicity analysis with brachytherapy using cobalt 60 source. All insertions were done when patient had completed EBRT and fit for intracavitory insertions. All patients were available for final analysis

CHARACTERISTICS

AGE (TABLE-5.1)

AGE [Years]	Number of patients [percentage]
30- 40 yrs	01 [3%]
41 -50 yrs	10 [27%]
51-60 yrs	18 [49%]
61 -65 yrs	08 [21%]

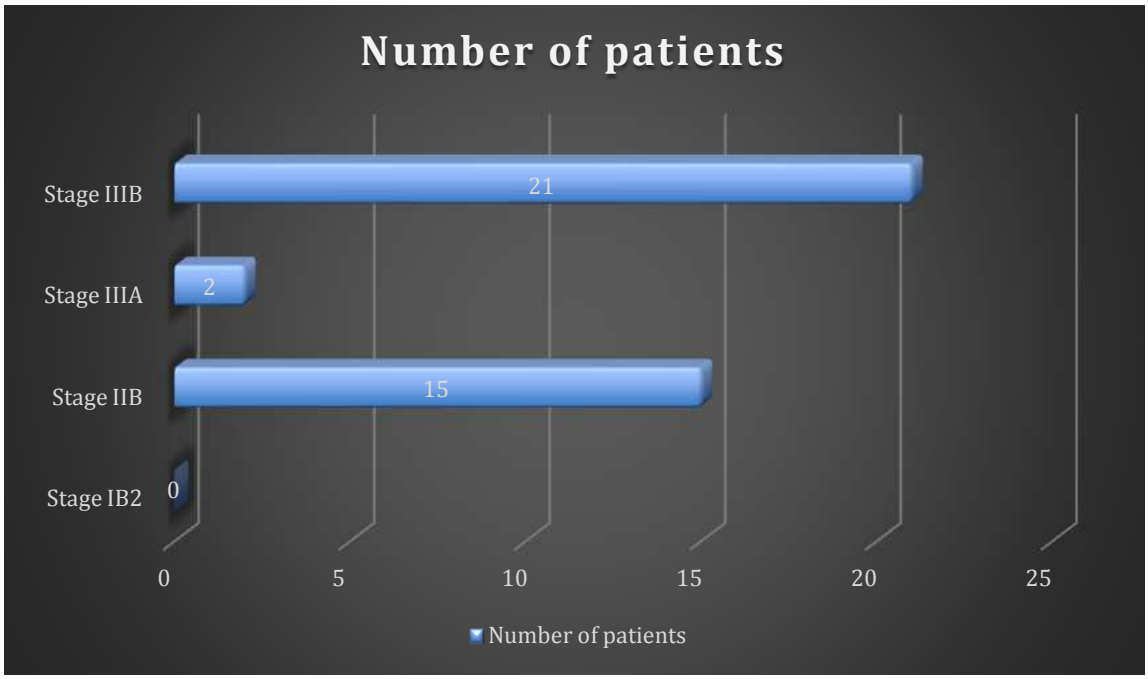
FIGURE [5.1]



FIGO STAGING (TABLE - 5.2)

STAGE	NUMBER OF PATIENTS [%]
IB2	NIL
IIB	15 [39.4%]
IIIA	02 [5.2%]
IIIB	21 [55.2%]

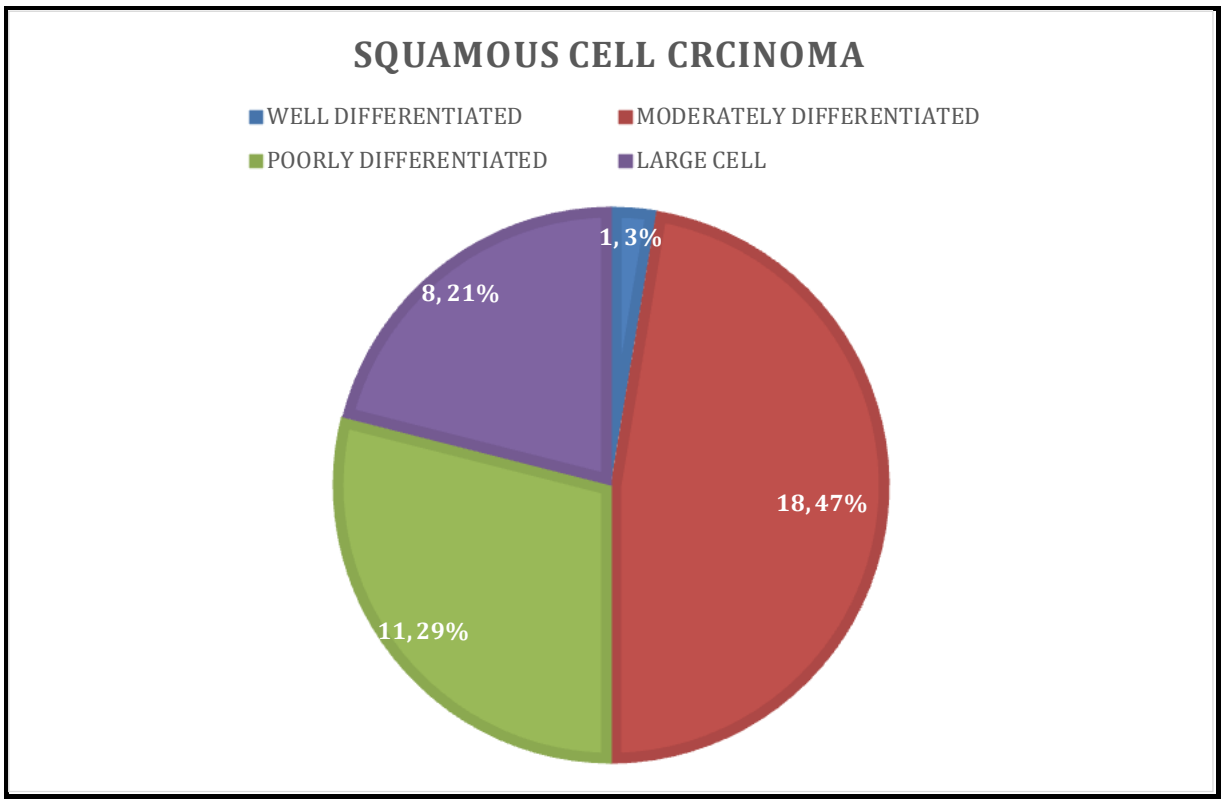
FIGURE-5.2



Histology (Table- 5.3)

SQUAMOUS CELL CARCINOMA	NO.OF PATIENTS
WELL DIFFERENTIATED	01 [2.6%]
MODERATELY DIFFERENTIATED	18 [47.3%]
POORLY DIFFERENTIATED	11 [29%]
LARGE CELL NON KERATINIZING	08 [21%]

FIGURE-5.3



EBRT+CHEMO (Table-5.4)

EBRT+CHEMO	NUMBER OF PATIENTS
RT+CHEMO	38
RT ONLY	NIL

TIME INTERVAL BETWEEN EBRT AND BRACHYTHERAPY

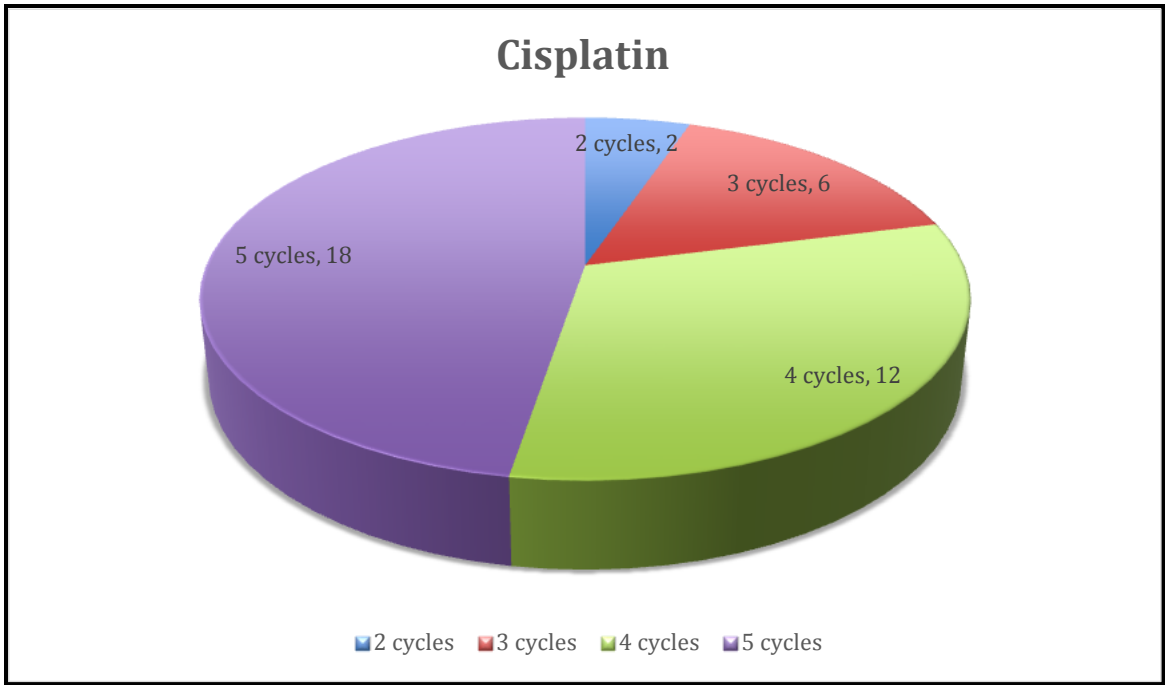
(Table - 5.5)

TIME INTERVAL	NUMBER OF PATIENTS [%]
< 1 WEEK	23 [60.5%]
>1 WEEK	15 [39.4%]

CHEMOTHERAPY CYCLES (Table - 5.6)

CISPLATIN [CYCLE]	NUMBER OF PATIENTS	PERCENTAGE
2 CYCLES	02	5.2%
3 CYCLES	06	15.7%
4 CYCLES	12	31.5%
5 CYCLES	18	47.36%

FIGURE-5.4

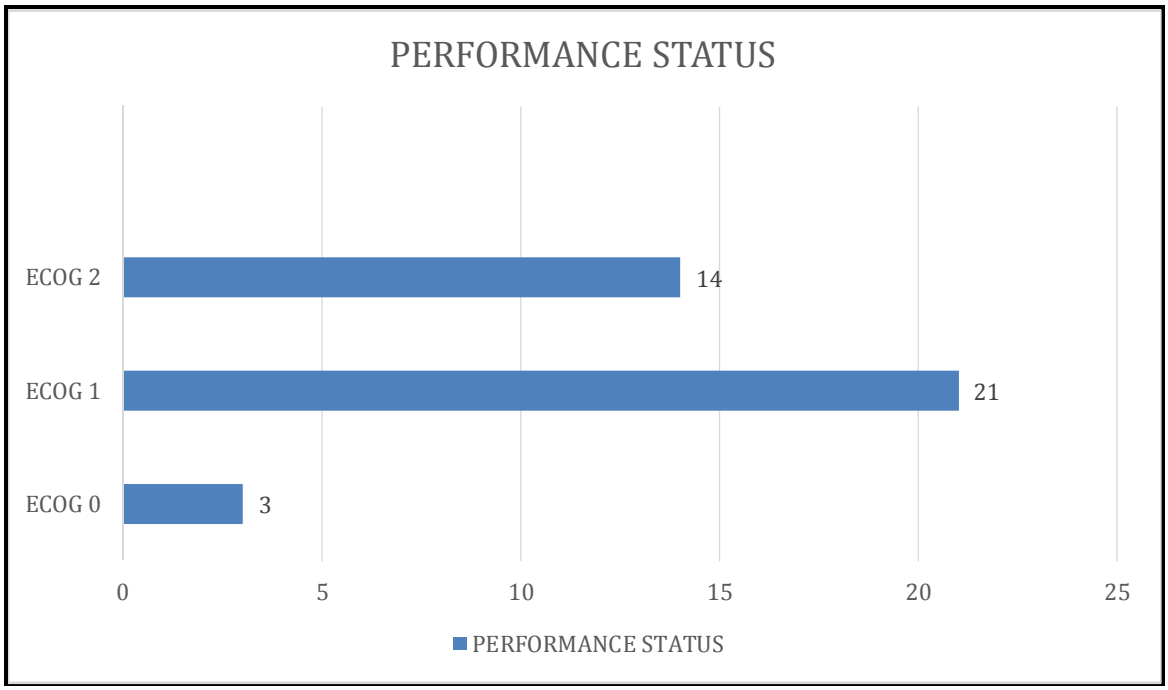


Majority of the patients in the study were able to tolerate chemotherapy cycle and were able to complete all 5 weekly schedules.

PERFORMANCE STATUS (Table-5.7)

ECOG	NO.OF PATIENTS
0	03 [7.8%]
1	21 [55.2%]
2	14 [36.8%]

FIGURE-5.5



There was a delay of more than a week to 12 days for nearly half of the patients due to grade 3 - 4 skin reactions due to EBRT and referral from other centers but this was compensated with twice weekly brachytherapy with a minimum gap of 72 hrs between each fractionation.

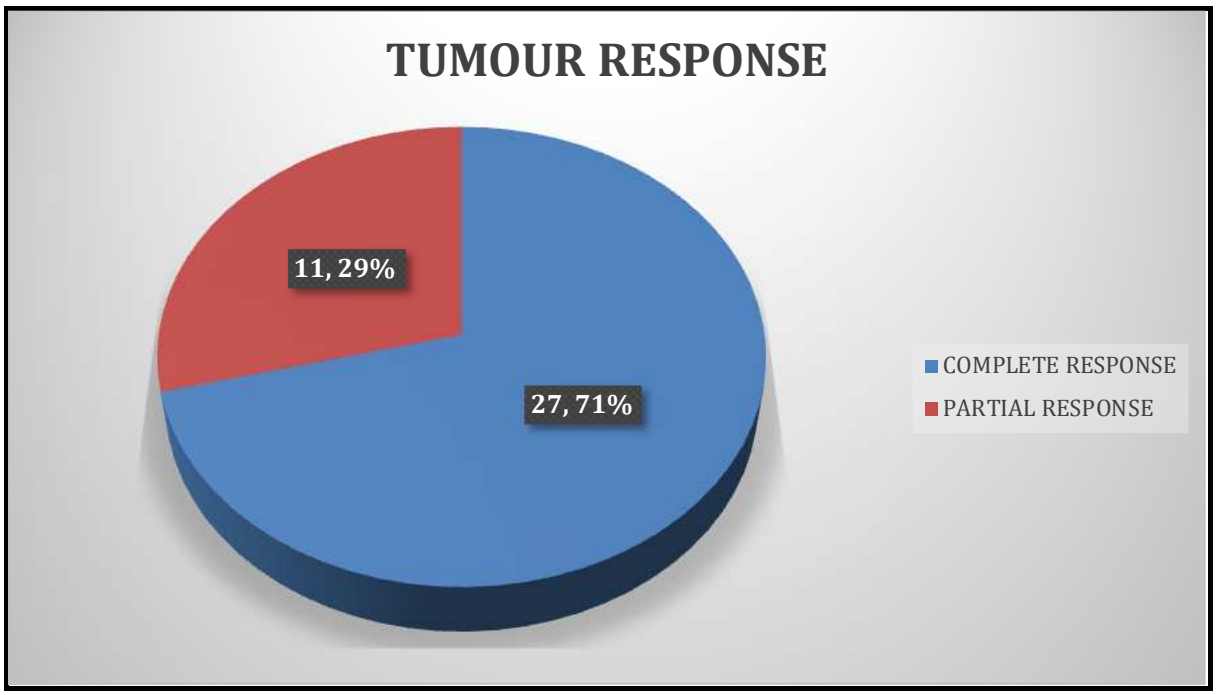
SECONDARY ASSESMENT

There was no patient related factors for delay in between the fractions except for 1 patient who had grade III GI toxicity and was managed with symptomatic and supportive care.

TUMOUR ASSESMENT AFTER EBRT (Table- 5.8)

TUMOUR RESPONSE [CLINICAL]	NUMBER OF PATIENTS
COMPLETE RESPONSE	27 [71%]
PARTIAL RESPONSE	11 [29%]

FIGURE-5.6



BRACHY THERAPY DOSE CHARACTERISTICS. (Table-5.9)

CA CERVIX[1-III]	MEDIAN	RANGE
EBRT[WHOLE PELVIS]	50GY	45-50 GY
HDR	7/3#	-
PT A	7gy	7-7.5GY
ICRU BLD PT	5.6GY	4.2-6GY
ICRU REC PT	5.4GY	3.2-6GY
BED RECT[EBRT+HDR]	124.4	120-133
EQD2 TUMOUR[EBRT+HDR]	83.6GY	78.8-86GY

REACTIONS ASSESED

- NAUSEA
- VOMITING
- DIARRHEA
- URINARY FREQUENCY
- URINARY URGENCY

(Table- 5.10)

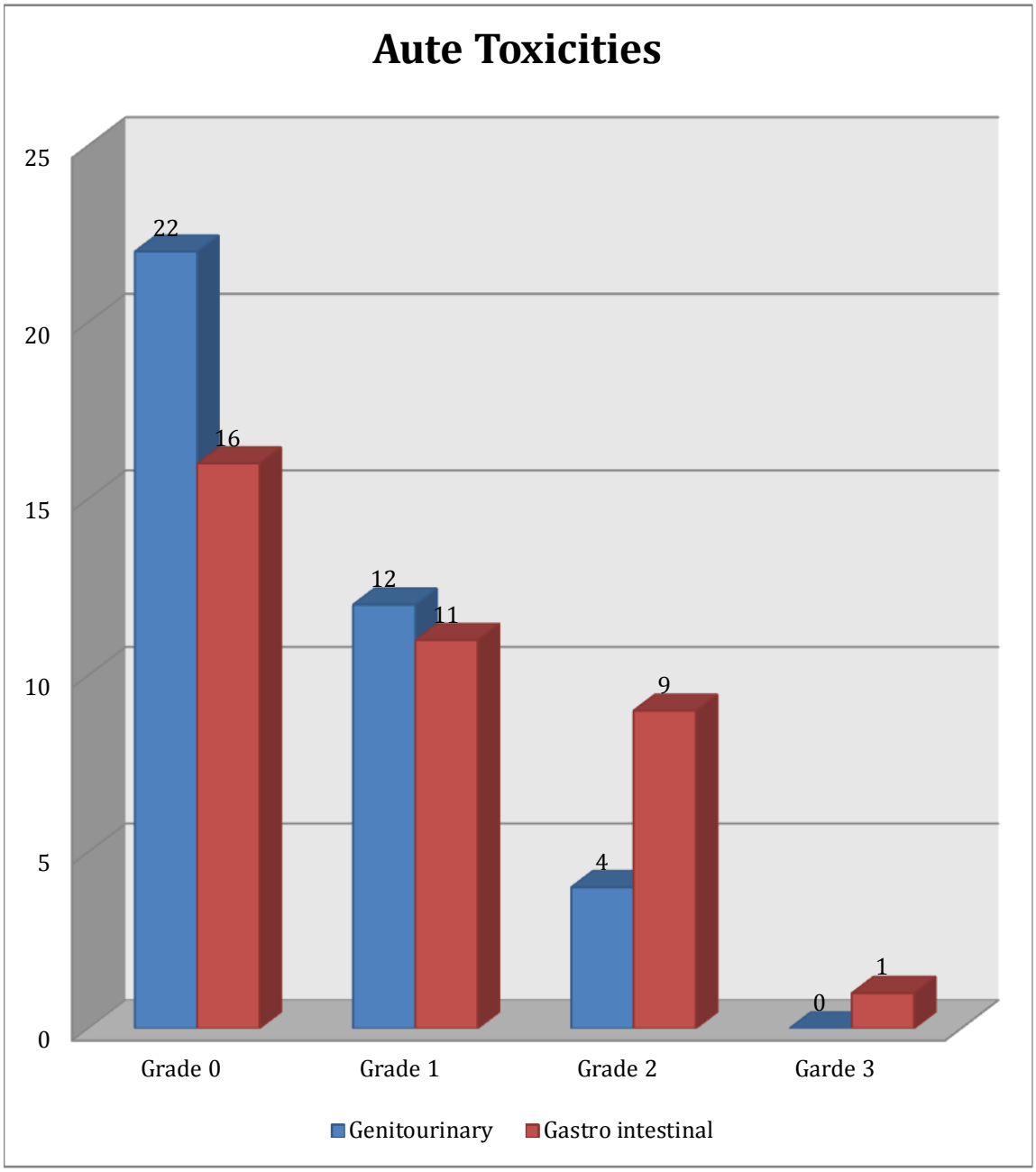
GENITOURINARY TOXICITY [RTOG acute toxicity scale]

GENITO URINARY	NO.OF PATIENTS	PERCENTAGE
GRADE 0	22	55.2 %
GRADE 1	12	31.5 %
GRADE 2	04	10.52%

GASTROINTESTINAL TOXICITY **(Table- 5.11)**

GI TOXICITY	NO.OF PATIENTS	PERCENTAGE
GRADE 0	16	42.1%
GRADE 1	11	28.94%
GRADE 2	09	23.68%
GRADE 3	01	2.63%

FIGURE 5.7


Aute Toxicities
25
20
15
10
5
0
22
16
12
11
4
9
0
1
Grade 0
Grade 1
Grade 2
Garde 3
Genitourinary
Gastro intestinal

DISCUSSION

Atara ntekim[51] et al compared the acute gastrointestinal and genitourinary Toxicity associated with Co-60 source in the brachytherapy of cervical cancer. His study assessed 70 patients with cervical cancer who received 45 Gy in 22 fractions of pelvic external beam radiotherapy and 19.5 Gy in 3 fractions of HDR with Co-60 source using tandem and ring applicators with 6 courses of cisplatin 50 mg/m2 and 5 fluorouracil 1000 mg/m2. (3%) had grade 3 gastrointestinal toxicity while all others had grade 2 toxicity.

Jain Abhay Kumar et al[52] studied 65 patients of carcinoma cervix for acute toxicity using cobalt brachytherapy .all patients completed EBRT 45-50GY/ 180-200 CGY /#/25 #/ 5 days a week using telecobalt machine followed by intracavitory application after 1 week. 7gy in 3 # were given and toxicity assessed by CTCAE 4.03 version. Only 2 patients [3%] had acute diarrhea. This was comparable to iridium source.

Montien Pesee et al[53] did a retrospective study of uterine cervical cancer patients, stages IB-IVB treated by radiotherapy alone. The patients received teletherapy 50Gy / 25 fractions, five fractions per week to the whole pelvis together with HDR Cobalt -60 after loading brachytherapy of 850 cGy/ fraction weekly to point A for 2 fractions for 141 patients of cervical cancer. 96.5% had complete response rates but morbidity rates of grade1 and grade 2 radiation

proctitis of 27.0%, and 10.6 % were reported .The grade 1 and grade 2 radiation cystitis were reported as 1.4%, and 1.4 %. Grade 3 radiation complications were 0.71% of radiation proctitis and 0.71% small bowel obstruction . The mean onset time to develop radiation proctitis after treatment was 15 months with a range of 6-61 months, for radiation cystitis it was 30 months (range 9 - 47 months) and for small bowel obstruction it was 53 months. So treatment with HDR-60 brachytherapy less than 850 cGy per fractionation for decreasing the grade 2 and grade 3 radiation morbidity was recommended in the study.

Om Prakash Gurjar et al[54] *reported* the dosimetric parameters of Co-60 based high dose rate (HDR) brachytherapy plans for patients of carcinoma uterine cervix .study on ten patients with locally advanced carcinoma of the uterine cervix . Computed tomography (CT) images were taken after three channel applicator insertions. The planning for 7 Gray per fraction (7 Gy/#) was done for Co-60 HDR brachytherapy following the American Brachytherapy Society (ABS) guidelines. All the patients were treated with 3# with one week interval between fractions The mean dose to high risk clinical target volumes (HRCTV) for D90(dose to 90%volume) was found to be 102.05% (Standard Deviation (SD): 3.07). the mean D2cc (dose to 2cubic centimeter volume) of the bladder, rectum and sigmoid were found to be 15.9 Gy (SD: 0.58), 11.5 Gy (SD: 0.91) and 4.1 Gy (SD: 1.52), respectively. The target coverage and doses to organs at risk (OARs) were achieved as per the ABS guidelines. This study concluded

that the Co-60 HDR brachytherapy unit is a good choice especially for the centers with a small number of brachytherapy procedures as no frequent source replacement is required like in an Ir-192 HDR unit.

Upendra Nandwana et al[55] examined the dosimetry of intracavitary radiotherapy (ICRT) in carcinoma of the cervix using cobalt-60 (Co-60) as source of ICRT, and as an alternative to iridium-192 (Ir-192) retrospectively. The study was done on 80 ICRT patients. . The dose to point A, 60 Gy isodose reference volume, and bladder and rectum maximum and mean doses were defined. It was found that dosimetry of Co-60 as a brachytherapy source was consistent with the International Commission on Radiation Units (ICRU 38) recommendations. Co-60 is a logical alternative to Ir-192 in low socio-economic settings when repeated changing of the source is not an option.

Thanatip Tantivatana et al[56] did a retrospective cohort study of patients with cervical cancer and treated with radiotherapy Ir-192 group and cobalt-60 group. The 2- and 5-year disease-free survival rate in Ir-192 group were 80.4% and 73.1% and in Co-60 group were 82.5% and 74.7%, respectively (p=0.365). Overall survival rates at 2 and 5 years were 89.4% and 77% of the Ir-192 group, and 91.6% and 81.9% in the Co-60 group, respectively (p=0.238). The complications were primarily grade 1 or 2. Grade 3 and 4 complications were found in 13 of 274 and 7 of 206 in Ir-192 and Co-60 groups, respectively

(p=0.232). Grade and clinical stage of cancer significantly affected the survival outcome. patients who were treated with HDR Co-60 brachytherapy were comparable in survival and toxicity outcomes of those with HDR Ir-192 brachytherapy concluding Co-60 source has economic advantages over Ir-192 and hence suitable for low resource setting.

Stefan Strohmaier et al[57] compared the isotopes ^{60}Co and ^{192}Ir as radiation sources for high-dose-rate (HDR) afterloading brachytherapy in view of availability with identical geometrical dimensions. The paper compared the characteristics of both nuclides in different fields of brachytherapy .It investigated the advantages or disadvantages of both radionuclides for HDR brachytherapy due to their physical differences. Results of this work showed that no advantages or disadvantages exist for ^{60}Co sources compared to ^{192}Ir sources with regard to clinical aspects. Nevertheless, there are potential logistical advantages of ^{60}Co sources due to its longer half-life (5.3 years vs. 74 days), making it an interesting alternative especially in developing countries.

Y. Lee et al[58] investigated that dose rate (HDR) brachytherapy contributed about 7% of the total Equivalent Dose in 2-Gray Fractions (EQD2) of external beam radiation therapy (EBRT) and HDR brachytherapy .Due to the location in the pelvis and subsequent distance from the implant, LN groups receive differing amounts of brachytherapy contribution. . Twenty-one patients with 45

positive pelvic LNs (9common iliac (CI), 15 external iliac (EI), 12 internal iliac (II) and 9 obturator (Ob) LNs) treated in two institutions from Oct 2007 to Aug 2011 were included in this retrospective analysis. All patients received EBRT to the pelvis with a supplemental boost to the involved pelvic node, plus HDR brachytherapy. Pathologically involved LNs were contoured on the planning EBRT image as well as the 4 to 5 brachytherapy planning images. The mean received dose of each LN from the EBRT and brachytherapy plans was recorded and EQD2 was calculated .brachytherapy EQD2 was significantly different among 4 pelvic LN groups. The average prescribed doses from the EBRT, including the initial pelvic fields and boost contribution to CI, EI, II and Ob LNs, were 54.60Gy, 54.53Gy, 53.15Gy and 54.42Gy respectively. The average prescribed HDR doses to International Commission on Radiation Units and Measurements (ICRU) point A were 26.83Gy, 27.84Gy, 29.79Gy and 28.49Gy accordingly. The average dose delivered to CI, EI, II and Ob LNs were 53.19Gy, 55.14Gy, 53.26Gy and 55.10Gy (EBRT), and 2.65Gy, 4.31Gy, 5.46Gy and 5.77Gy (HDR) respectively, with the Corresponding EQD2 of 52.26Gy, 54.36Gy, 52.42Gy and 54.42Gy (EBRT), and 2.36Gy, 4.00Gy, 5.09Gy and 5.47Gy (HDR). The HDR contribution to CI, EI, II and Ob LNs was 4.10%, 6.93%, 8.83% and 9.48% of the total EQD2 (EBRT+HDR, 57.69Gy) of all LN groups respectively. There was a statistically significant difference in brachytherapy EQD2 among the 4 pelvic LN groups ($p < 0.05$), with the Ob LN receiving the most dose. This study highlights that there is

4.1% to 9.5% variation in brachytherapy dose contribution of the total EQD2 among pelvic LN groups. This difference in HDR contribution needs to be considered when prescribing EBRT boost dose to each pelvic LN group for the optimal therapeutic total dose.

Amir Shahram et al[59] *in l*ocally advanced stage did a cross sectional-analytic study to report outcome 154 patients with carcinoma of cervix treated with external beam radiation therapy (EBRT) and high dose rate (HDR) brachytherapy with cobalt 60 (Co-6o) remote after loading system. They were analyzed for three-year disease-free survival (DFS), three-year overall survival (OS) incidence of acute and late complications for HDR brachytherapy. Fourteen patients (9.1 %) were in Stage I (FIGO classification), 8 (5.2%) were in Stage IIA, 26 (16.9%) were in Stage IIB, 100 (64.9%) were in Stage III, and 6 (3.9 %) were in Stage IVA. The follow up duration was between - 60 months with a median of 38 months. Overall rectal and bladder treatment toxicity rates were 33.7%. The three-year DFS Rate was 85.7%, 70.7 %, 41% and 16.6% for Stages I, II, III, IVA.

DS Nikam,et al[60] reported the feasibility and cost effectiveness of high dose rate (HDR) cobalt60 (^{60}Co) source versus Iridium-192 (^{192}Ir) source brachytherapy in government funded hospitals and treatment interruption gap because of exchange of sources.it was a retrospective study of gynecological cancer

patients, The dates for ^{192}Ir sources installation and the last date and first date of brachytherapy procedure before and after source installation respectively were also analyzed and calculated the gap in days for brachytherapy interruptions where eight ^{192}Ir sources were installed. The mean gap between treatment interruptions was 123.12 days (range 1647 days). Around 52.25% of patients who received EBRT at their institute were referred to outside hospital for brachytherapy because of unavailability of Iridium source. The cost for 5 year duration for single cobalt source is approximately 20-22 lakhs while for Iridium sources is approximately 52-53 lakhs. This study concluded that the treatment interruption because of source exchange is longer and can be minimized by using cobalt source as it is cost effective and has 5 year working life. Thus, Co60 source for brachytherapy is a feasible option for government funded institutions.

Some of the studies that showed similar toxicity with iridium source were

Comparison of ≥III GI and GU acute toxicity in previous studies of chemo-radiation using Ir-192 and Co60 as HDR source [Table- 6.1]

Study	Hdr/FR	EBRT	EQD2	GI TOXICITY[%]	GU TOXICITY [%]
CHUNG et al 2005 [Iridium]	25/5	45/25	75.50	2	0
Chen et al 2006 [Ir192]	24/4	45/25	72.25	4.3	0
Shakespeare et al 2006	31.8/6	45/25	86.65	0	0
Atara netkim et al with co60 2008	19.5/6	45/22	70.25	3	0
Jain abhay kumar 2017[Co60]	21/3	50/25	79.75	3.07	0

COMPARISON OF EARLY < GRADE 2 TOXICITY IN PREVIOUS STUDIES [Table – 6.2]

STUDY	Proctitis	Diarrhea	Nausea	Vomiting	Cystitis	GU
CHUNG et al 2005	-	77	44	-	-	22
Chen et al 2006	-	-	-	-	-	5.7
Shakespeare et al 2006	4.8	-	-	-	23.8	-
AtaraNtekim et al 2008	57	59	11	10	40	40
Jain Abhay kumar 2017	56.92	58.46	10.76	13.84	38.46	40

Compared with these studies which used iridium and cobalt 60 for brachytherapy the acute toxicities were comparable with no significant grade III complications. Most patients had early symptoms .Only 1 patient had grade III GI toxicity.

Our study was comparable to Atara Ntkeim et al and Jain Abhay et al. Both these studies used cobalt 60 as the brachytherapy source for treatment.

In our study the average age group of presentation was 53 years where as it was 45 Years and 50 years in the above two studies. Majority of patients were stage IIIB. Predominant HPE was moderately differentiated squamous cell carcinoma. All patients had chemotherapy all though some of them could not complete all the 5 cycles.3 fractions of 7 Gy with a gap of 72 hrs between each fraction was a feasible option similar to Jain Abhay et al study and it compensated the time delay between EBRT and brachytherapy . Dose per fraction in our study was 7Gy as per ABS guidelines .Secondary end points were response rates of primary tumor .The acute toxicity profile was assessed using RTOG scale which differed from the above two studies who had used common Terminology Criteria for Adverse Events . All patients were able to complete the treatment within the 7 weeks though 1 patient who had grade III toxicity during brachytherapy could not. 35 [92.1%] patients had complete clinical and radiological response at the end of 3 months.

PRE TREATMENT CT SCAN (FIGURE 6.1)

POST TREATMENT CT SCAN [EBRT +ICA] AT 8 WEEKS [fig -6.2]

CONCLUSION

Cervical cancer is the third most common malignancy in women worldwide of which 85% are detected in developing countries. According to GLOBOCON 2018 in INDIA, it is the second most common malignancy among women. Carcinoma cervix turn over accounts for 10-15% in our hospital with additional patients being referred for brachytherapy from most government hospitals in Tamil Nadu. A shorter overall treatment time in treating this malignancy would result in better patient compliance as long as there is no increased toxicity or loco regional failure. This study highlighted the fact that use of cobalt radionuclide brachytherapy has comparable toxicity profile as Iridium source .This in turn would translate to treat large number of patients in low resource settings with high patient load with no frequent change of source as cobalt 60 has long half-life with similar dosimetric properties and acute toxicity profile. The follow up period of this study was limited to 90 days post treatment .Further follow up is needed to assess the late toxicity effects of cobalt brachytherapy.

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Annexure 1:

INFORMATION TO PARTICIPANTS

Title: PROSPECTIVE STUDY OF HIGH DOSE RATE BRACHYTHERAPY IN CERVICAL CANCER TREATMENT USING COBALT 60 RADIONUCLIDE SOURCE.

Name of Participant:

Name of the Principal(co–investigator): DR.S.B.MEENAKSHI.

Name of the institution: Department of radiotherapy, RGGGH, MMC.

You are invited to take part in this research/ study/procedures/tests. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of research?

- Cervical cancer is one of the leading cancers in women.Concurrent chemoradiation is a treatment modality with established benefits in both organ preservation and survival. Brachytherapy increases the tumor dose while decreasing the dose to organ at risk [bladder,rectum].
- ^{60}CO radionuclide source has similar dosimetric properties with comparable levels of gastrointestinal and genitourinary toxicity as that of ^{192}Ir source.
- More over source replacement of ^{60}Co takes 5-8 years once which is beneficial in low resource and high patient load settings.
- Chemotherapy with weekly cisplatin is a more acceptable regimen than three weekly cisplatin with 5flourouracil.Hence cisplatin 40mg/m^2 was used in this study.
- Radiotherapy will be delivered by anteroposterior field or four field box technique with a telecobalt machine in the form of
- External beam radiotherapy 45-50gy/25-28#/180-200cgy/#/5 days a week to the whole pelvis.

  Followed by intracavitary brachytherapy using ^{60}Co radionuclide source 7gy/#/3# with a minimal gap of 72 hrs between each fraction.

  Remaining dose will be given as parametrial boost using external beam radiotherapy if required.

We want to test the efficacy and acceptable levels of toxicity of " Using High dose rate brachytherapy in cervical cancer treatment using cobalt 60 radionuclide source".

- We have obtained permission from the Institutional Ethics Committee.

The study design

Single arm prospective study

Study Procedures

The study involves evaluation of outcomes with High dose rate brachytherapy in cervical cancer using cobalt 60 radionuclide source. chemotherapy in the form of injection weekly will be given once .blood test, urine examination ,clinical examination and other necessary tests will be carried out. These tests are essential to monitor your condition and to asses the safety and efficacy of the treatment given to you.
In addition, if you notice any physical or mental change(s), you must contact the persons listed at the end of the document.
You may have to come to the hospital (study site) for examination and investigations apart from your scheduled visits, if required.

Possible benefits to other people

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required.
The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

Signature of Investigator Signature of Participant Date Date

Annexure 2:

INFORMED CONSENT FORM

TITLE OF THE STUDY: **PROSPECTIVE STUDY OF HIGH DOSE RATE BRACHYTHERAPY IN CERVICAL CANCER TREATMENT USING COBALT60 RADIONUCLIDE SOURCE** .

NAME OF THE PARTICIPANT:

NAMEOF THE PRINCIPAL (Co–Investigator): **DR.S.B.MEENAKSHI.**

NAME OF THE INSTITUTION: MADRAS MEDICAL COLLEGE

_____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in": **Prospective study of High dose rate Brachytherapy in Cervical cancer treatment using Cobalt 60 radionuclide source"**

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past 12 months including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study*
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.
8. I have not participated in any research study within the past 12month(s). *
9. I agree to undergo complete blood count, renal and liver function test, chest x ray, CT scan of the head and neck
10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital. *
11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent. *
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
13. I have understood that my identity will be kept confidential if my data are publicly presented

14. I have had my questions answered to my satisfaction.
15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____ Signature_____

Date_____

Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____

Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent

Name _____ Signature_____

Date_____

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To

Dr.S.B.Meenakshi
Post Graduate in M.D. Radiotherapy
Department of Radiation Oncology
Madras Medical College
Chennai 600 003

Dear Dr.S.B.Meenakshi,

The Institutional Ethics Committee has considered your request and approved your study titled **"PROSPECTIVE STUDY OF HIGH DOSE RATE BRACHYTHERAPY IN CERVICAL CANCER TREATMENT USING COBALT 60 RADIONUCLIDE SOURCE " - NO.09062017**

The following members of Ethics Committee were present in the meeting hold on **06.06.2017** conducted at Madras Medical College, Chennai 3

1. Prof.Dr.C.Rajendran, MD.,	:Chairperson
2. Prof.R.Narayana Babu,MD.,DCH., MMC,Ch-3	: Deputy Chairperson
3. Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4. Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
5.Prof.A.Pandiya Raj,Director, Inst. of Gen.Surgery,MMC	: Member
6.Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai	: Member
7.Prof. Susila, Director, Inst. of Pharmacology,MMC,Ch-3	: Member
8.Prof.K.Ramadevi,MD., Director, Inst. of Bio-Chemistry,MMC,Ch-3	: Member
9.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
10.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist
11.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

ஆராய்ச்சி தகவல் தாள்

சென்னை இராஜீவ் காந்தி அரசு பொது மருத்துவமனைக்கு வரும் புற்றுநோய் நோயாளிகளிடம் கதிர்வீச்சு சிகிச்சை பற்றிய ஆராய்ச்சி.

கோபால்ட்-60 மூலம் பயன்படுத்தி கர்பப்பை வாய் புற்றுநோய் சிகிச்சைக்கு அதிக அளவு விகிதம் உள்கதிர்வீச்சு சிகிச்சையினை பற்றி ஆராய்வது இந்த ஆராய்ச்சியின் நோக்கம்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் தீவிர கதிர்வீச்சு சிகிச்சை அளித்து சில சிறப்பு பரிசோதனைகளுக்கு உட்படுத்தி அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களது நோயின் தன்மையோ அல்லது சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக்கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு சிகிச்சையின் முடிவுகளை ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிக்கப்படும் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

நாள் :
இடம் :

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சி தலைப்பு

கோபால்ட்-60 மூலம் பயன்படுத்தி கர்ப்பப்பை வாய் புற்றுநோய் சிகிச்சைக்கு அதிக அளவு விகிதம் உள்கதிர்வீச்சு சிகிச்சையின் ஆய்வு

பெயர்	:	தேதி	:
வயது	:	உள் நோயாளி எண்	:
பால்	:	ஆராய்ச்சி சேர்க்கை எண்	:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கமும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை புரிந்துக்கொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

எனக்கு கோபால்ட்-60 மூலம் பயன்படுத்தி கர்ப்பப்பை வாய் புற்றுநோய் சிகிச்சைக்கு அதிக அளவு விகிதம் உள்கதிர்வீச்சு சிகிச்சையினை பற்றி ஆராய்வதற்கு சம்மதம் தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின்பேரில் நான் பங்கு பெறுகின்றேன். இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின் வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்துகொண்டேன்.

நான் கோபால்ட்-60 மூலம் பயன்படுத்தி கர்ப்பப்பை வாய் புற்றுநோய் சிகிச்சைக்கு அதிக அளவு விகிதம் உள்கதிர்வீச்சு சிகிச்சையினை பற்றிய ஆய்வுக்கான விவரங்கள் கொண்ட தகவல் தாளைப் பெற்றுக்கொண்டேன்.

எனக்கு இந்த ஆராய்ச்சியின்படி கதிர்வீச்சு சிகிச்சை எடுத்துக் கொள்ள சம்மதம். இந்த ஆராய்ச்சிக்கு தேவையான பிற பரிசோதனைகள் செய்துக்கொள்ள சம்மதம்.

நான் என்னுடைய சுய நினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக்கொள்ள சம்மதம் தெரிவிக்கிறேன்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

நாள் :

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CERTIFICATE

This is to certify that the dissertation entitled **“PROSPECTIVE STUDY OF HIGH DOSE RATE BRACHYTHERAPY IN CERVICAL CANCER TREATMENT USING COBALT-60 RADIONUCLIDE SOURCE”** of the candidate Dr.MEENAKSHI.S.B, with Registration Number **201619005** for the award of **M.D. Degree** in the Branch of **Radiotherapy**. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from Introduction to Conclusion pages and result shows **___ Percentage** of Plagiarism in the Dissertation.

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